Chronic Hepatitis C Treatment in the US: Current Status 2012

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AND

My presentation may possibly include discussion of off-label use of DAAs

Outline of this talk

- **Review Hep C 101: basic statistics**
- **Review the CDC Baby Boomer Directive**
- **Provide an overview to current Rx with the new DAAs**
- **Give a glimpse of the future, which happens to be just around the corner**

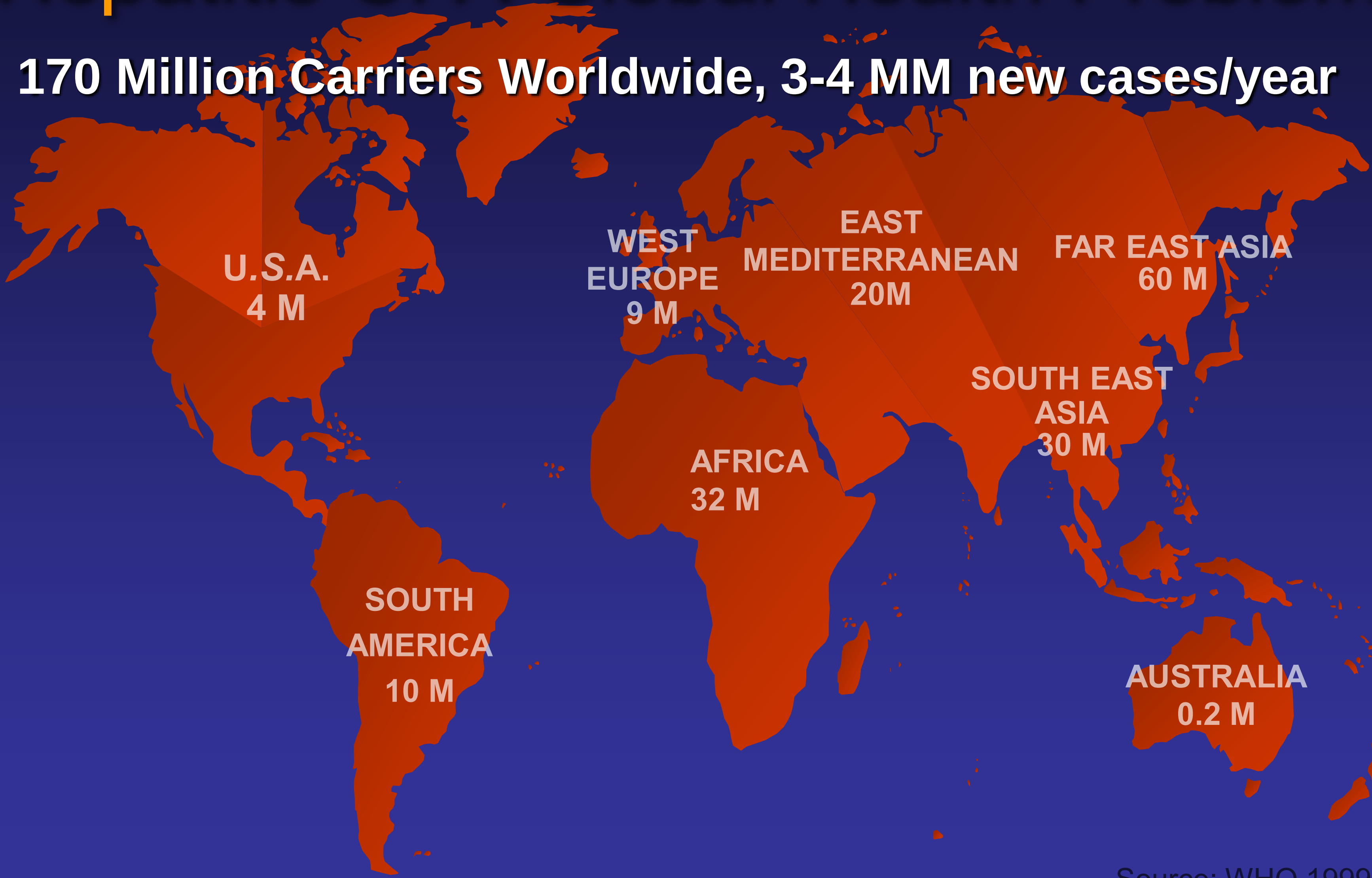
Hepatitis C Virus (HCV)

- **Discovered in 1989 as a small RNA blood-borne virus with a large reservoir of chronic carriers worldwide**
- **Major cause of post-transfusion hepatitis prior to 1992**
- **Major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide**
- **Prevalence is 1.8% of the US population, 4 million**
- **1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States**

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002.

Hepatitis C: A Global Health Problem

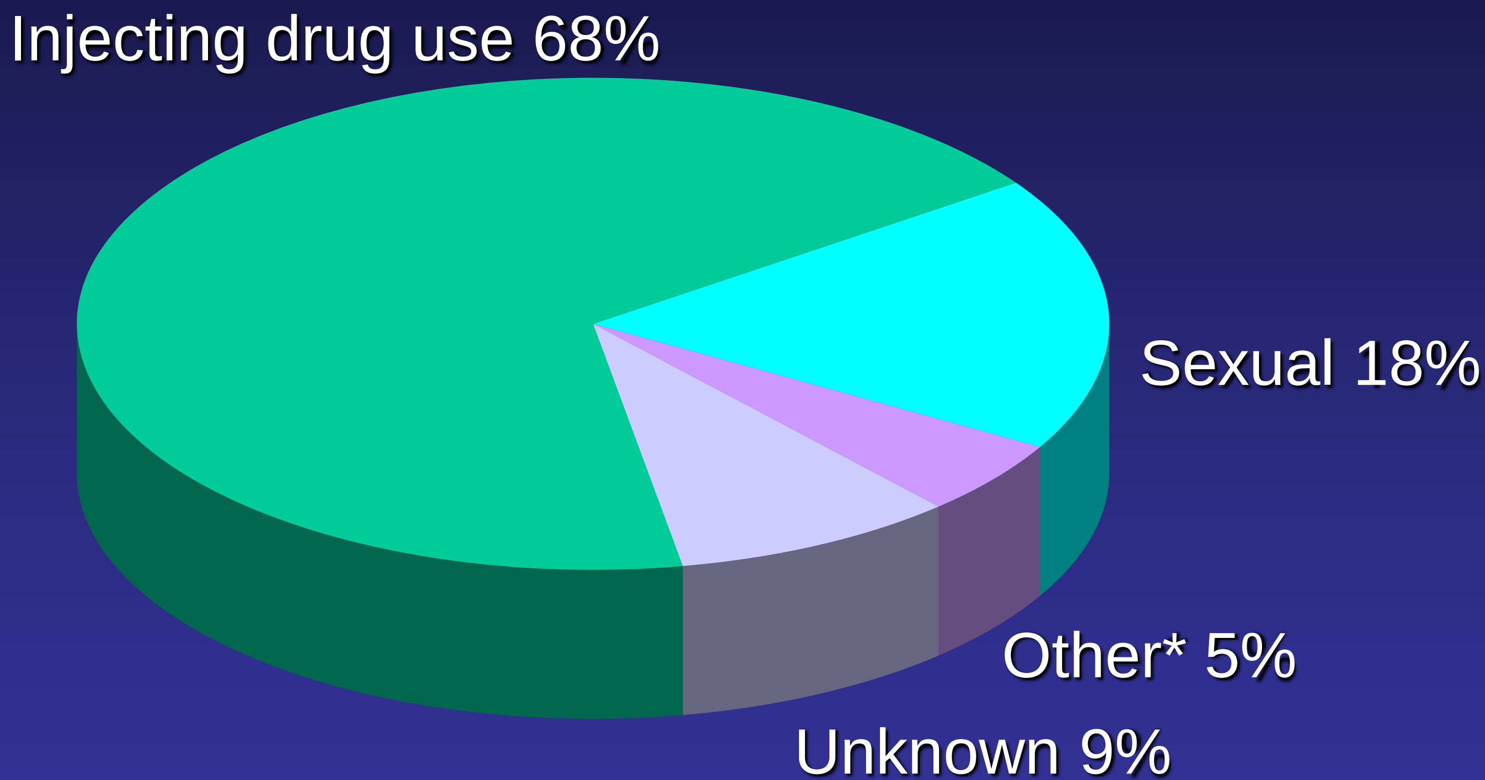
170 Million Carriers Worldwide, 3-4 MM new cases/year



Source: WHO 1999.

Sources of Infection for Hepatitis C

(1995-2000)



*Nosocomial; Health-care work; Perinatal

Adapted from Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/ Accessed 01/18/03. Alter MJ. *Hepatology* 2002;36:S93-S98.

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 61 / No. 4

August 17, 2012

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/conted.html.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Recommendations for Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945-1965

- Adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.

- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, <u>followed by referral to appropriate care and treatment services</u> for HCV infection and related conditions.

AASLD recommends considering antiviral treatment for HCV-infected persons with histological signs of bridging fibrosis, septal fibrosis, or cirrhosis (*18*). In 2011, the first generation of direct-acting antiviral agents (DAAs), the HCV NS3/4A protease inhibitors telaprevir and boceprevir, were licensed in the United States for treatment of HCV genotype 1(the most common genotype in the United States). Compared with conventional pegylated interferon and weight-based ribavirin therapy (PR) alone, the addition of one of these two protease inhibitors in clinical trials increased rates of sustained virologic response (SVR) (i.e., viral clearance following completion of treatment) from 44% to 75% and 38% to 63%, respectively, in persons with HCV (*50,51*). In a study of veterans with multiple co-morbidities, achieving an SVR after treatment was associated with a substantial reduction in risk for all-cause mortality of >50% (*52*) and substantially lower rates of liver-related death and decompensated cirrhosis (i.e., cirrhosis with the diagnosis of at least one of the following: ascites, variceal bleeding, encephalopathy, or impaired hepatitis synthetic function) (*18*). Because of the recent introduction of these treatment regimens, the long-term effects of DAA treatment in clinical practice have yet to be established, and the benefits might be different in community settings. In addition to the new Food and Drug Adminstration (FDA)-approved medications, approximately 20 HCV treatments (protease and polymerase inhibitors) are undergoing Phase II or Phase III clinical trials (*53*); treatment recommendations are expected to change as new medications become available for use in the United States.

Consideration of a New HCV Testing Strategy

Because of the limited effectiveness of risk-based HCV testing, the rising HCV-associated morbidity and mortality, and advances in HCV care and treatment, CDC has evaluated public health strategies to increase the proportion of infected persons who know their HCV infection status and are linked to care. Several analyses of nationally representative data have found a disproportionately high prevalence of HCV infection among persons who were born during the mid-1940s through the mid-1960s. In an analysis of 1988–1994 NHANES data,

antibody among persons in the 1945–1965 birth cohort was 3.25% (95% CI = 2.80–3.76); persons born during these years accounted for more than three fourths (76.5%) of the total anti-HCV prevalence in the United States (*3*).

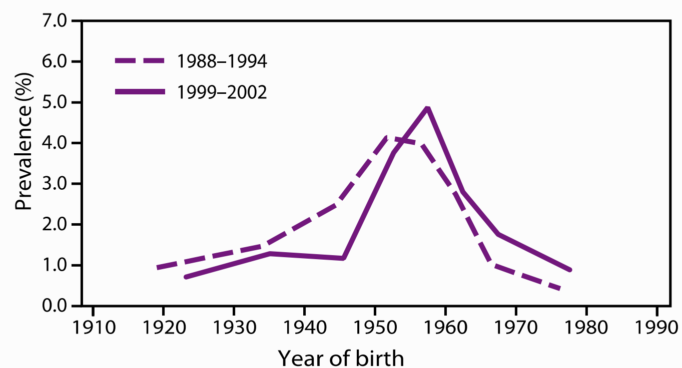
Selection of a Target Birth Cohort

To select a target birth cohort for an expanded testing strategy, CDC considered various birth cohorts with increased HCV prevalence (Table 1). For each proposed cohort, CDC

FIGURE 1. Prevalence of hepatitis C virus antibody, by age at time of survey — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002

Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Internal Med 2006;144:705–14. Modified and reprinted with permission from Annals of Internal Medicine.

FIGURE 2. Prevalence of hepatitis C virus antibody, by year of birth — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002



veighted, unadjusted anti- nd the size of the population. of HCV prevalence and ne 1945–1965 birth cohort e target population. Three 945–1965, 1950–1970, were additionally stratified and sex (Table 2). The he male-to-female ratio tial and were not critical irth cohort. However, the evalence by race/ethnicity n cohorts is notable. Both and 1945–1970 cohorts evalence of HCV-infected ack populations than the rt. Of the 210,000 anti- ersons in the 1945–1949 nately 71,000 (35%) were black. Because ck populations account for a substantial 1945–1965 birth cohort, these birth years better address this health disparity.

ng the possibility of including persons born) with the target population (i.e., 1945–1965 termined that such a strategy would direct imately 20 million additional persons at a tely $1.08 billion, resulting in identification 00,000 persons with chronic infection. The o screen to avert a single HCV-related death 945–1965 birth cohort compared with the cohort (607 and 679, respectively). Data

TABLE 1. Number and prevalence of persons born during 1945–1970 positive for anti-HCV and with chronic HCV infection, by birth cohort — National Health and Nutrition Examination Survey, United States, 1999–2008

Birth cohort	U.S. population (in millions)*	Anti-HCV No. (in millions)	Anti-HCV (Weighted %)†	Chronic HCV infection No. (in millions)§	Chronic HCV infection (%)
1945–1965	84.2	2.74	(3.25)	2.06	76.6
1950–1970	89.2	2.89	(3.24)	2.17	80.6
1945–1970	105.1	3.15	(3.00)	2.36	87.3
1950–1965	68.3	2.47	(3.61)	1.85	69.9
1950–1960	45.6	1.83	(4.01)	1.37	52.3
1945–1949	13.2	0.21	(1.58)	0.16	6.7
1966–1970	20.9	0.41	(1.94)	0.30	10.8

Abbreviations: HCV = hepatitis C virus; anti-HCV = antibody to hepatitis C virus.
* Source: U.S. Census Bureau. 2010 Census: Single years of age and sex: summary file 1, table PCT12. Available at http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_SF1_PCT12&prodType=table. Accessed April 27, 2012.
† Not adjusted by age or other covariates.
§ An estimated 75% of anti-HCV–positive persons have chronic HCV infection. (Source: Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. [Practice Guideline.] Hepatology 2009;49(4):1335–74.)

TABLE 2. Prevalence of anti-HCV among three birth cohorts, by sex and race/ethnicity* — National Health and Nutrition Examination Survey, United States, 1999–2008

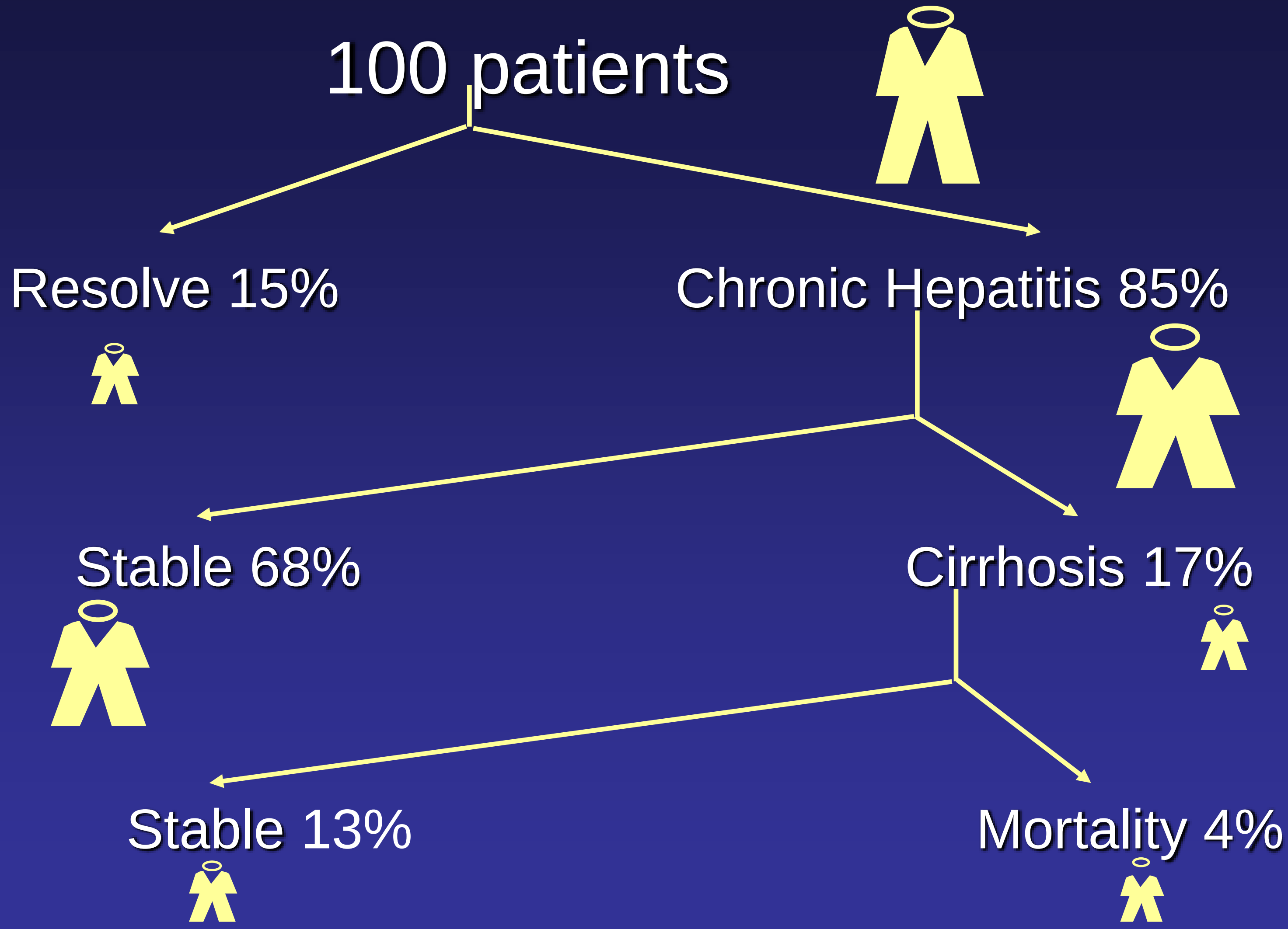
Characteristic	Anti-HCV (weighted %) 1945–1965	1950–1970	1945–1970
Sex			
Male	4.34	4.12	3.89
Female	2.19	2.34	2.14
Race/ethnicity			
White, non-Hispanic	2.89	3.01	2.77
Black, non-Hispanic	6.42	5.73	5.60
Mexican American	3.26	2.56	2.71

Abbreviation: anti-HCV = antibody to hepatitis C virus.
* Not adjusted by age or other covariates.

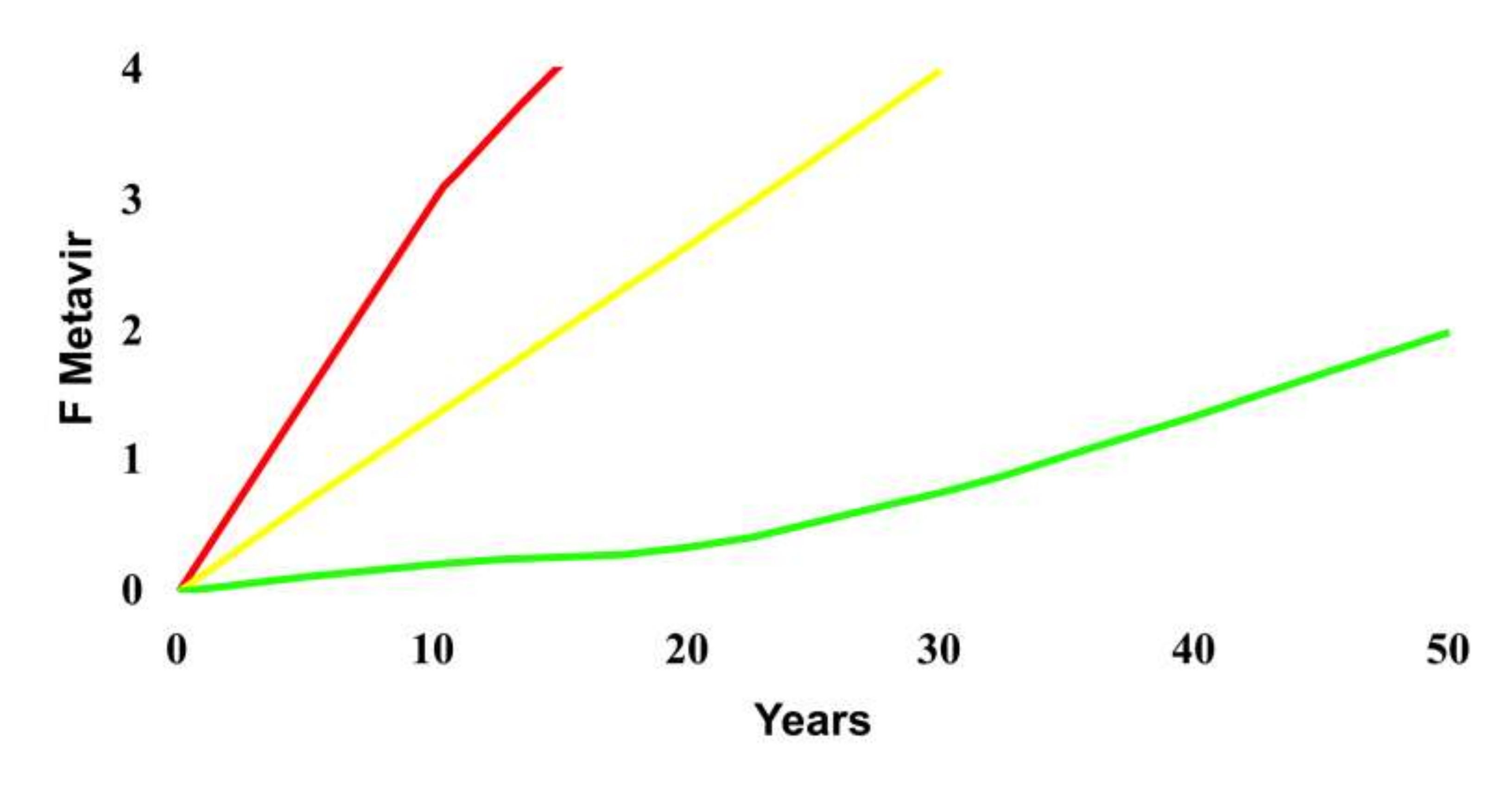
Summary of new CDC Recs

- **Current estimates are ca. 4 million Americans with HCV**
- **Between 45 and 85% of HCV infected are unaware of it**
- **Risk-based strategies have failed**
- **Baby boomers (1945-1965) represent 27% of the population but 75% of those infected**
- **1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States**

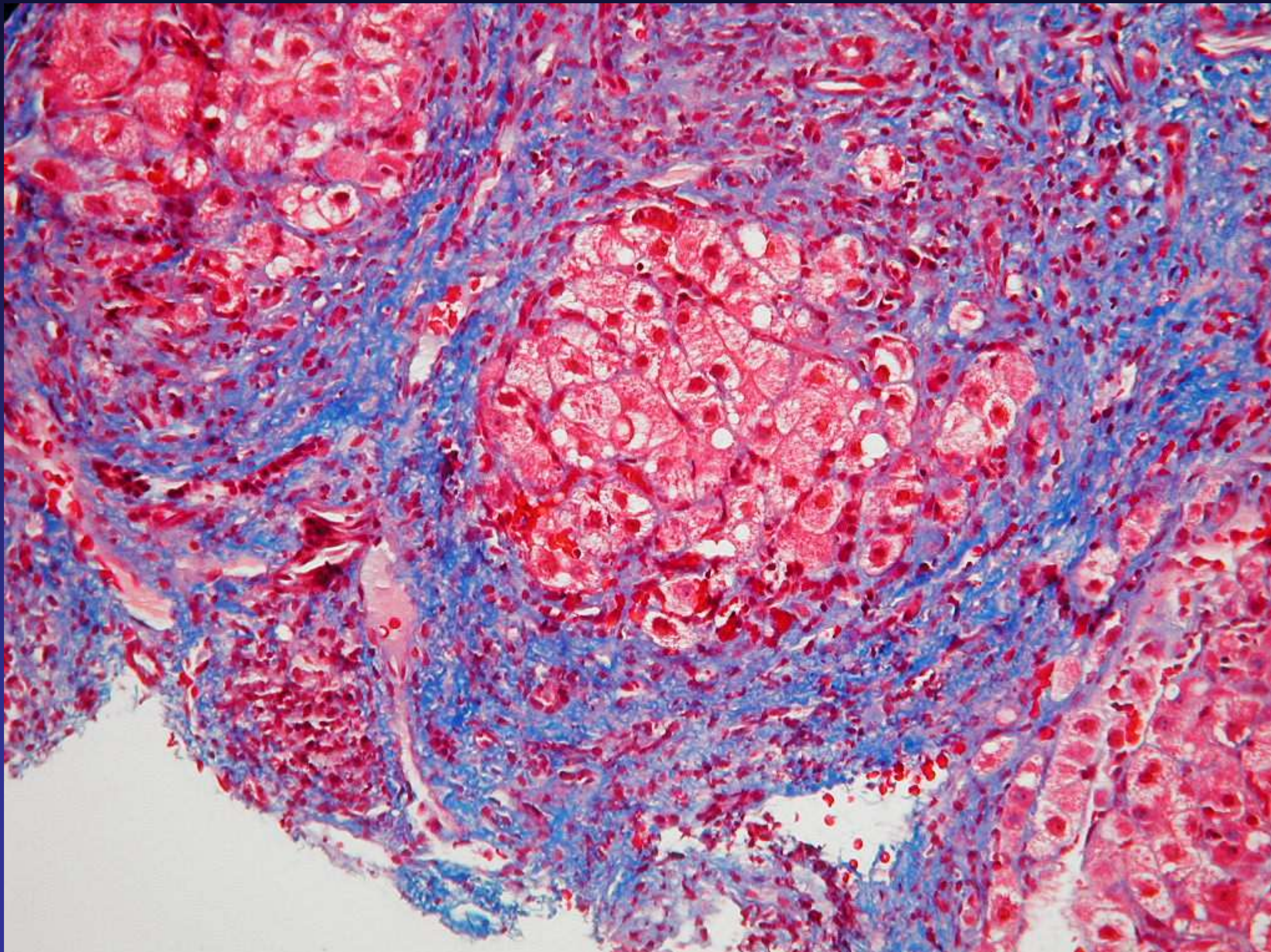
Natural History Hepatitis C



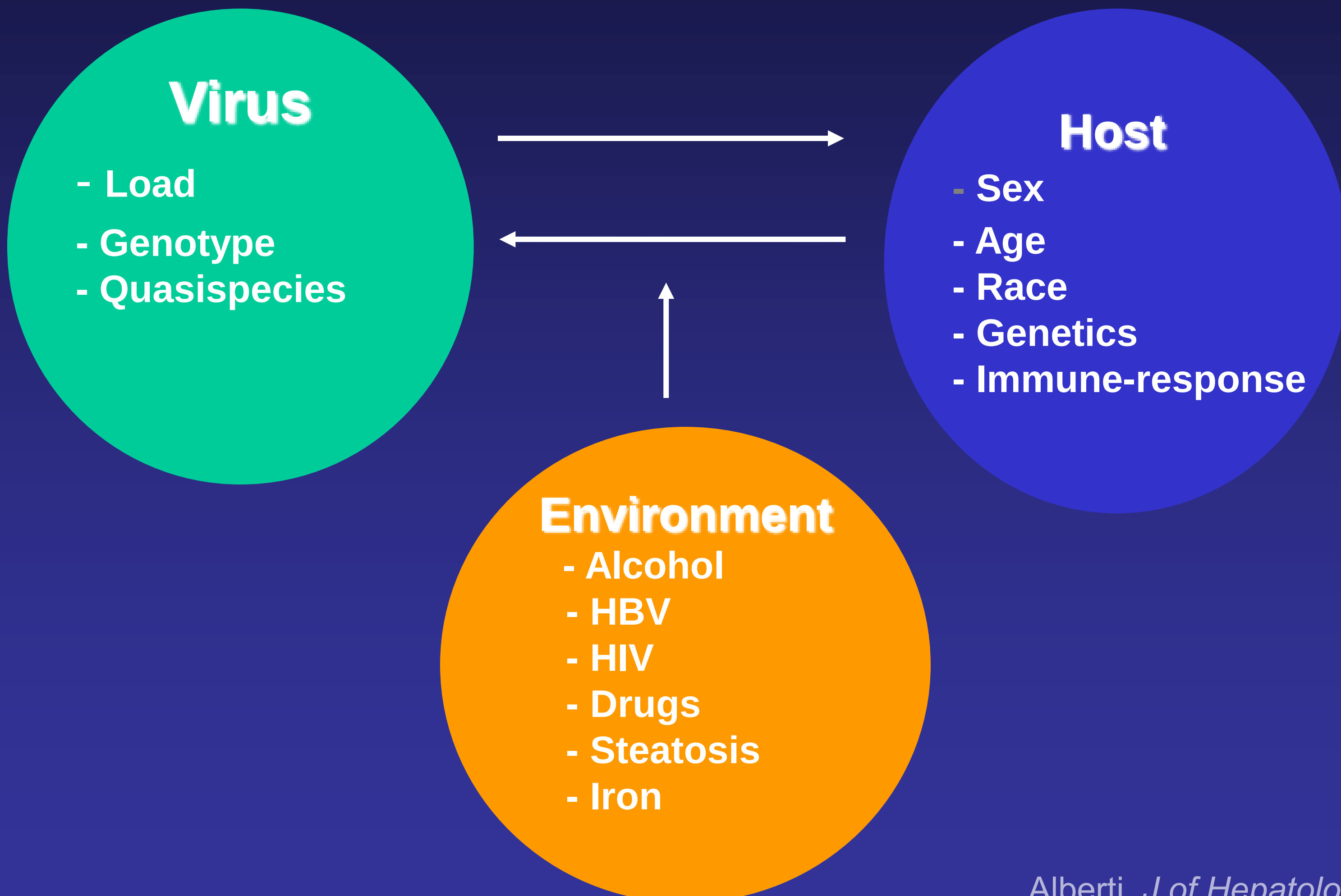
Modeling of Liver Fibrosis in Chronic Hepatitis C, n=1157 Patients



Poynard et al, Hepatology 1999

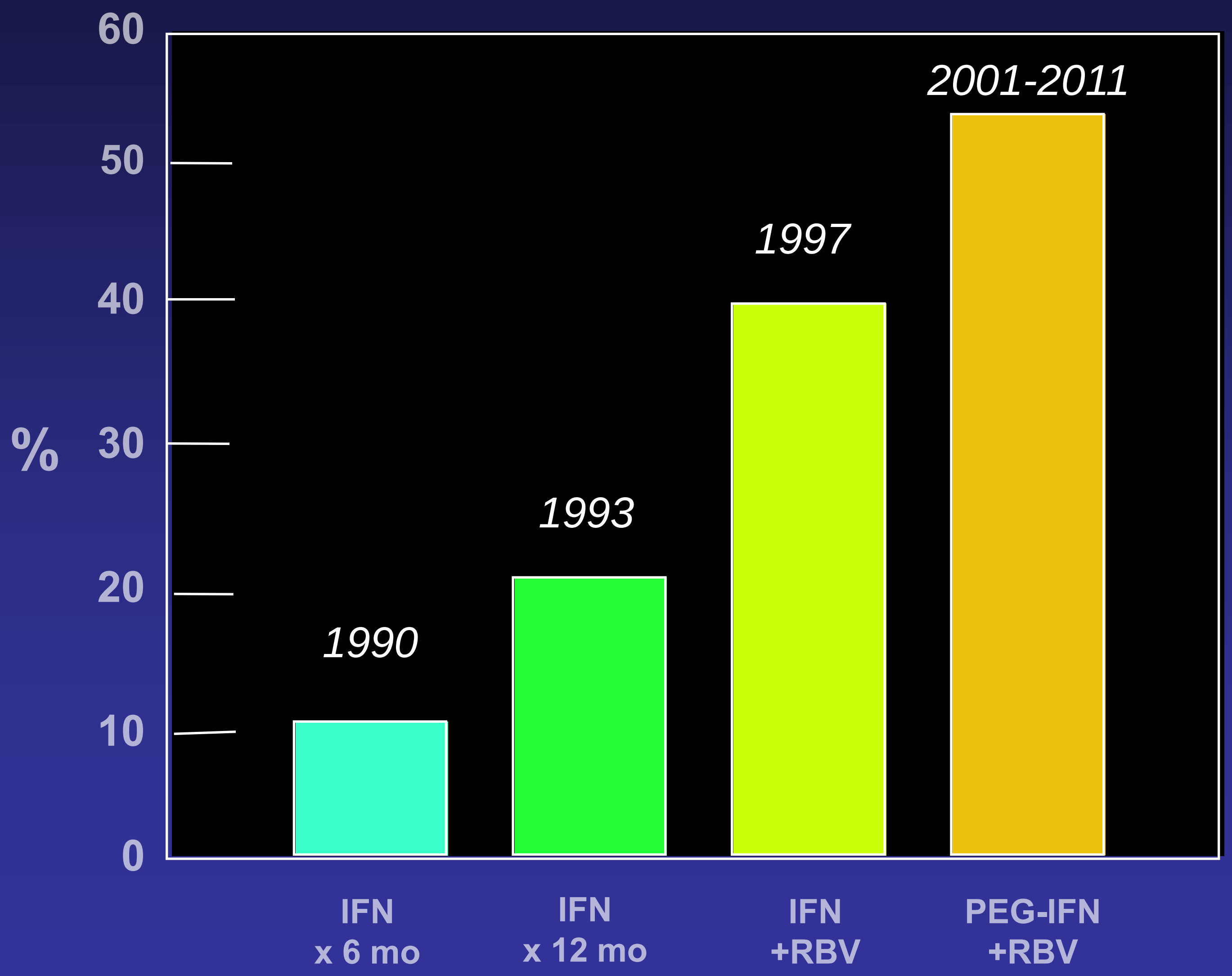


Factors Which Might Influence The Outcome Of Hepatitis C

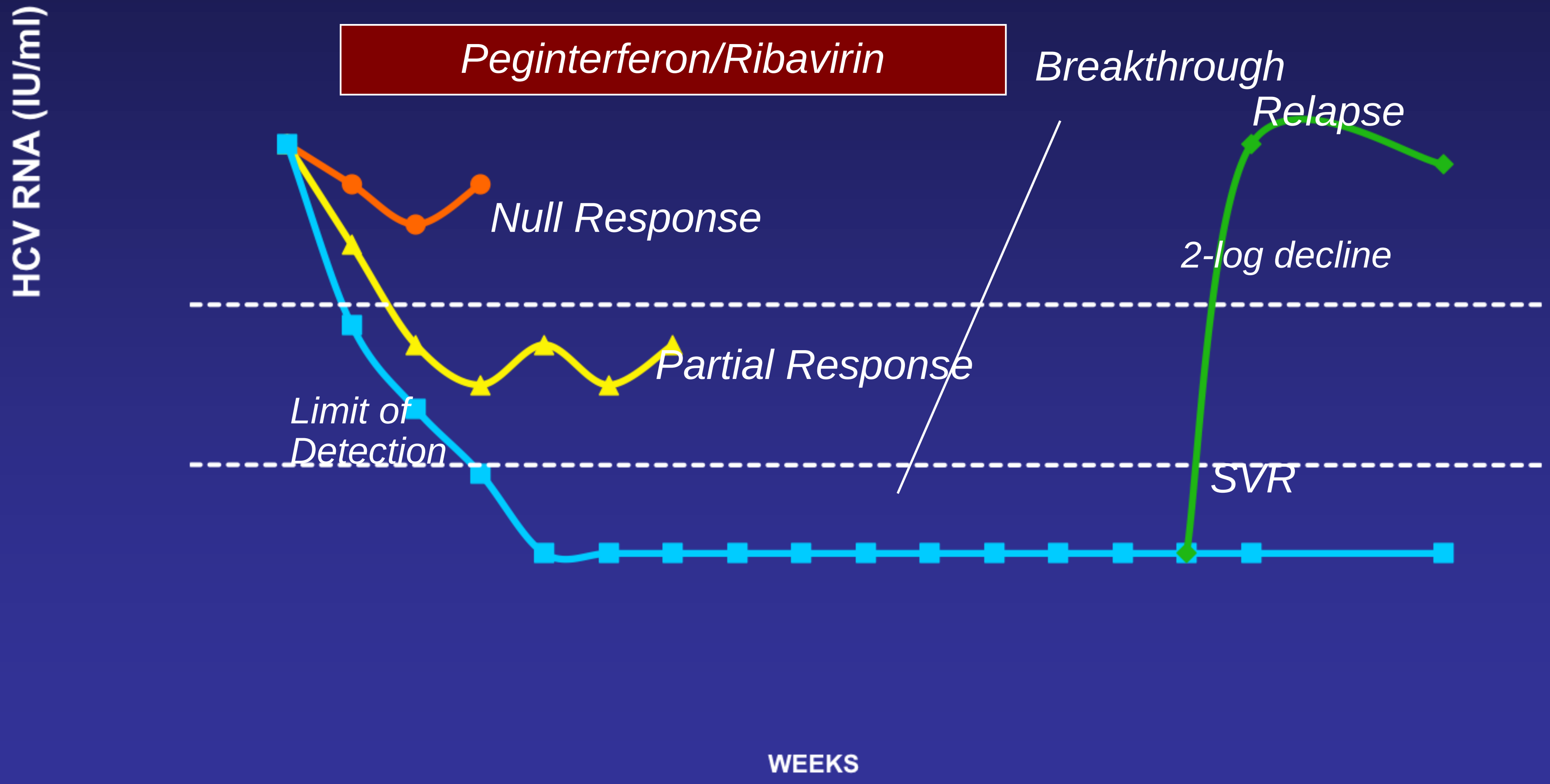


Alberti. *J of Hepatology*, 1999.

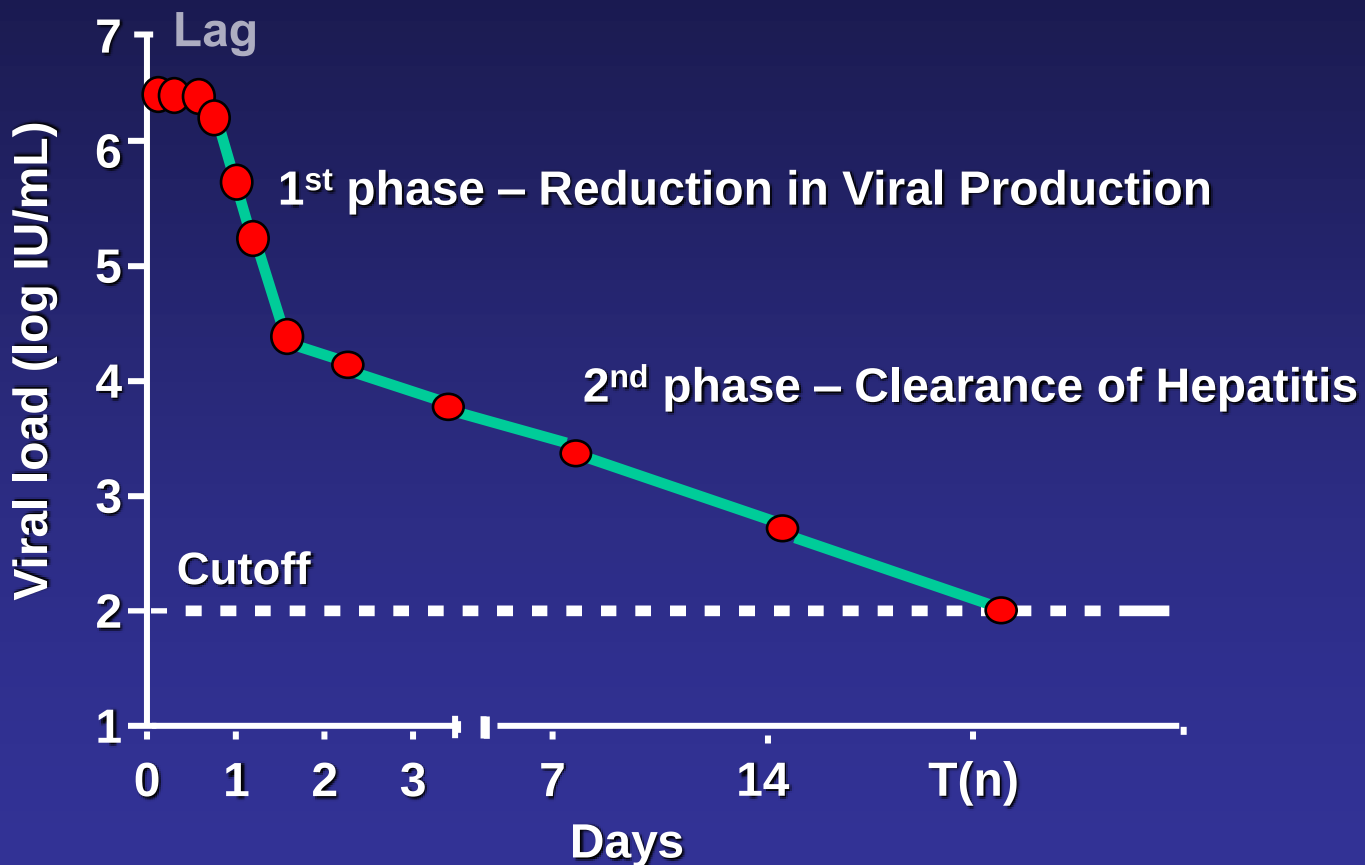
Advances in HCV Therapy
Average SVR



Treatment of Chronic HCV
Type of Response

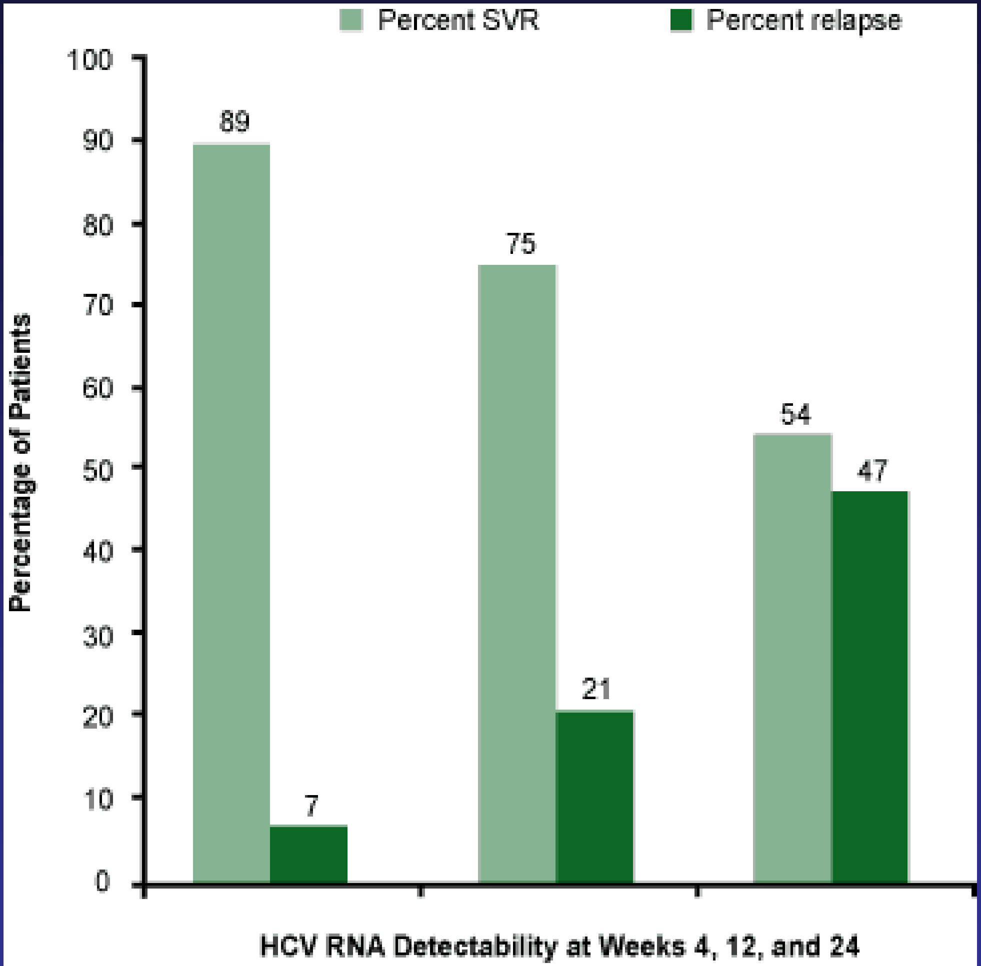


HCV Kinetics: Key to Viral Clearance



Neumann et al. *Science.* 1998;282:103.

Genotype 1: Relationship of SVR rate and time to undetectable HCV RNA.



Week 4	Undetectable	Detectable	Detectable
Week 12	Undetectable	Undetectable	Detectable
Week 24	Undetectable	Undetectable	Undetectable
n	112	156	51

Likelihood of RVR: 34% low VL vs. 23% with high VL

Both viral load and early response make a difference

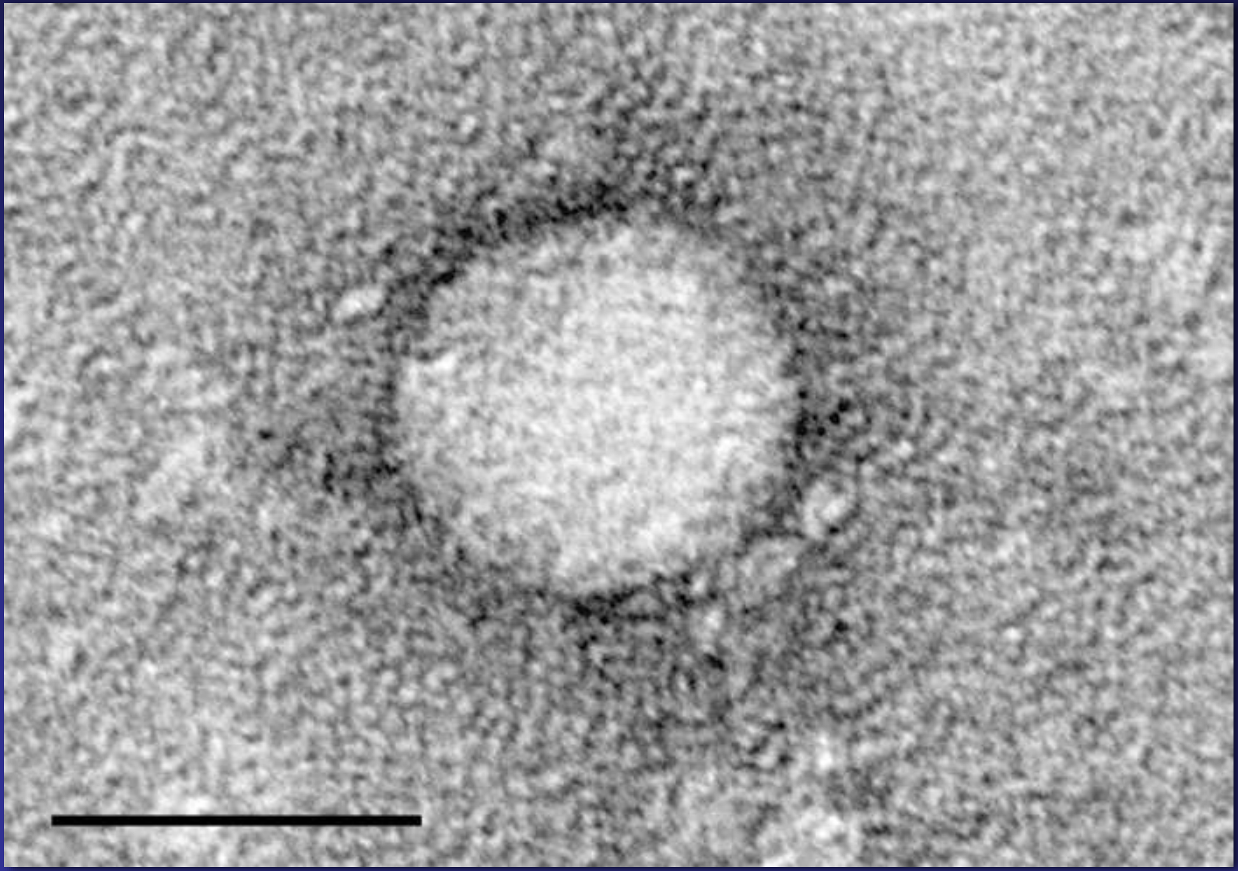
Overall response of Genotype 1: ca. 40% But ca. 25% in A-A patients

Ferenci et al Data based on Pegasys licensing trial

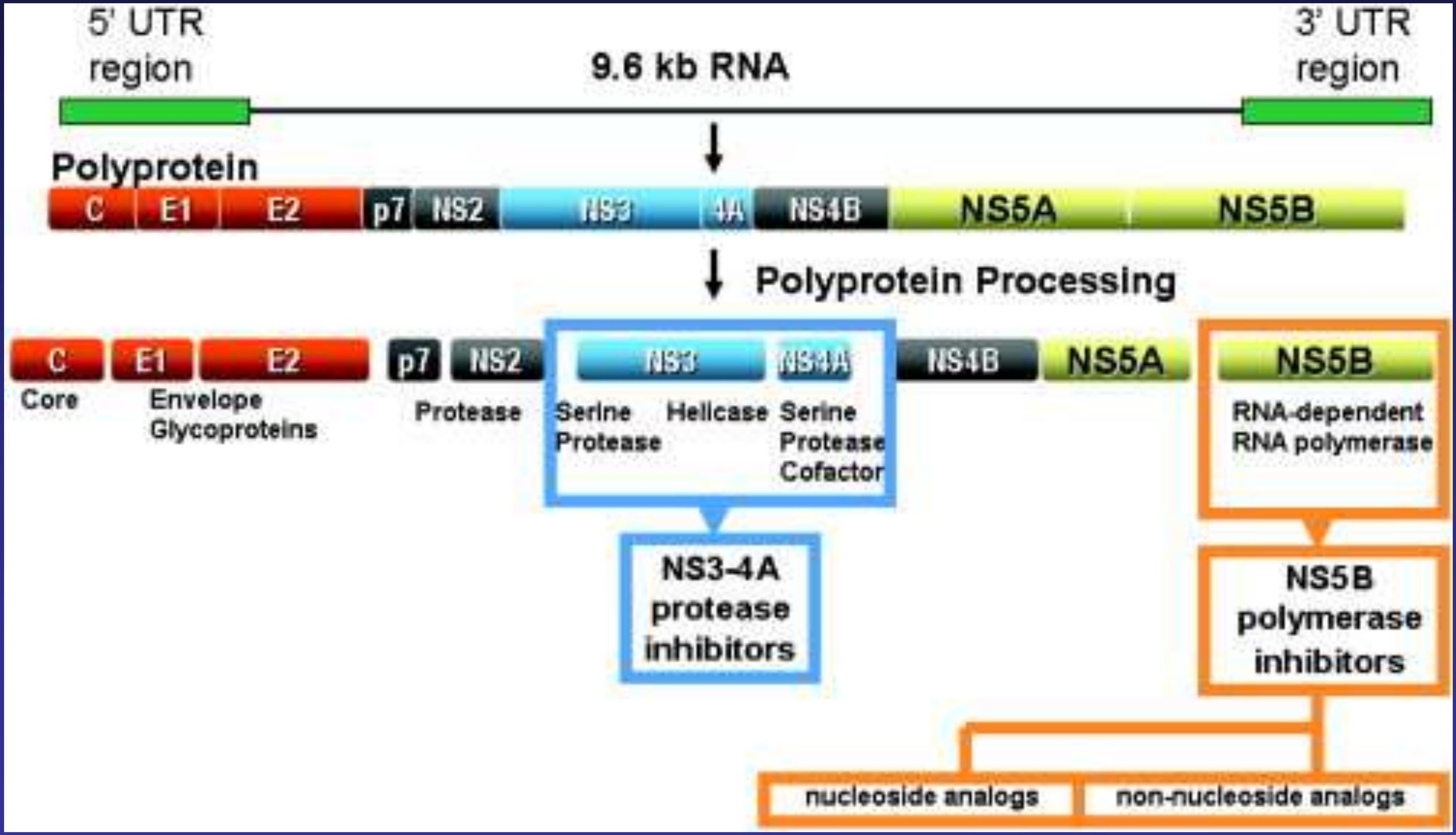
Virological Response Terms

- EVR = minimum 2 $\log_{10}$ decrease in HCV RNA during first 12 wk of therapy
- ETR = undetectable HCV RNA at the completion of therapy
- SVR = persistently undetectable HCV RNA for $\geq$6 months following completion of therapy
- RVR = negative at wk 4
- eRVR = extended RVR, neg wk 4 + wk 12, 20
- VRVR = negative at wk 1

Hepatitis C Virus

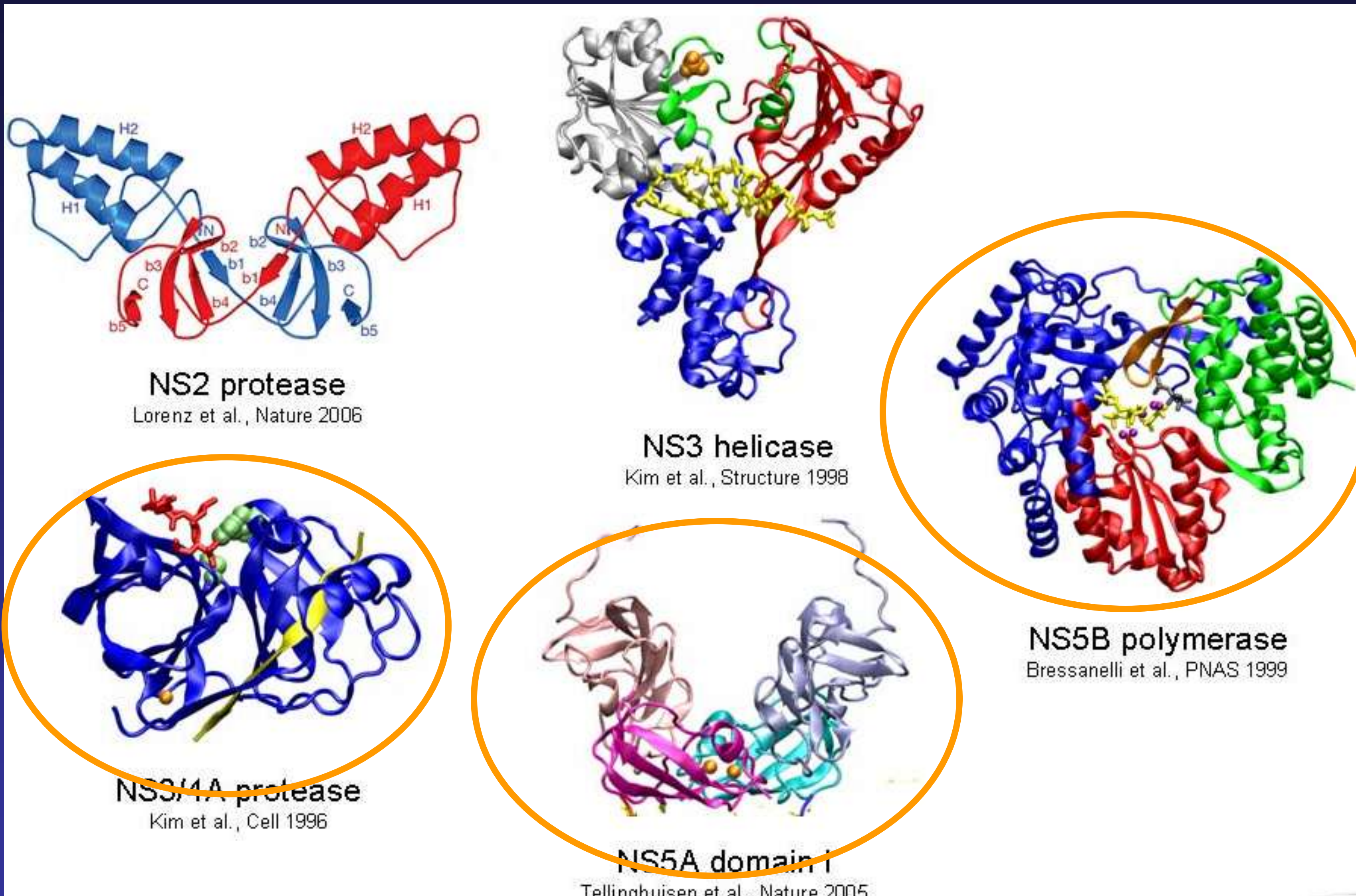


HCV Polyprotein Processing and Viral Protein Function



McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

Potential HCV Targets



Adapted from Bartenschlager RJ. Presented at 43rd EASL Milan, Italy, April 2008.

Graveyard for HCV Compounds is Filling Up Quickly!

ISIS 14803
(Antisense)

UT-231B
(Imino sugar)

Heptazyme
(Ribozyme)

VX-497
(IMPDH inhibitor)

ANA975
(TLR agonist)

BILN 2061
(Protease)

JTK-003
(Polymerase)

HCV-796
(Polymerase)

NM-283
(Polymerase)

R803
(Polymerase)

CPG 10101
(TLR agonist)

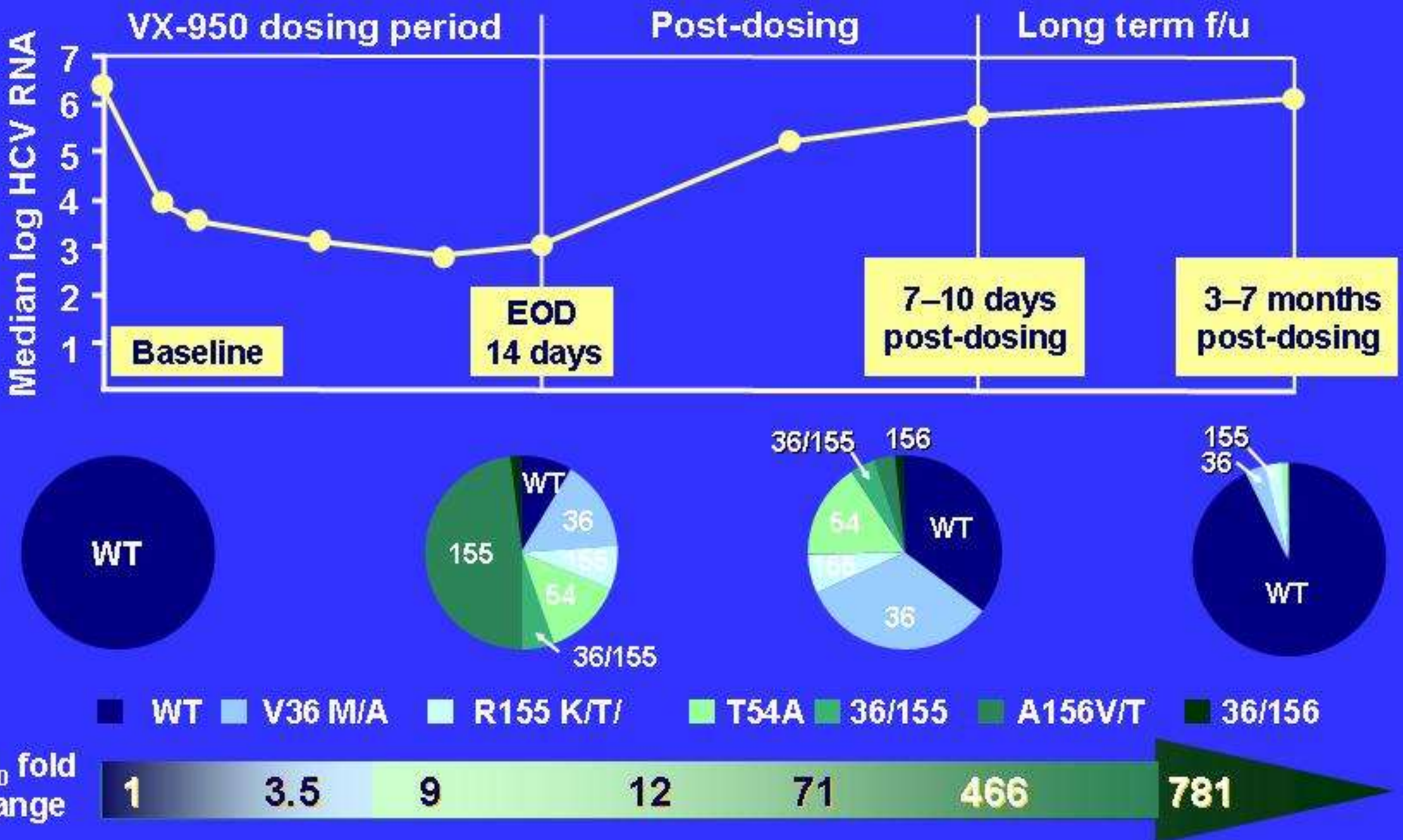
ACH-806/GS-9132
(NS4a)

R7025
(Interferon-alpha)

Data have not been reviewed or approved by FDA.

Courtesy of Nelson D.

Emergence of Resistance Underlies Breakthrough and Plateau Response



Data have not been reviewed or approved by FDA.

Sarrazin C, et al. *Gastroenterol.* 2007;132:1767-1777.

Back Up

Major HCV Therapy Trials 2006-2011

MERCK: Boceprevir, Victrelis®

SPRINT-1: Naïve, Phase 2: Boceprevir: dose finding

SPRINT-2: Naïve, Phase 3: Boceprevir: RGT/Blacks/Non-Black

RESPOND-2: Experienced, Phase 3: Boceprevir, length Rx experienced

VERTEX: Telaprevir, Incivek®

PROVE-1: Naïve, Phase 2: Telaprevir, dose/duration

PROVE-2: Naïve, Phase 2: Telaprevir, leave off RBV?

ADVANCE: Naïve 8 vs 12 wk, Phase 3: Telaprevir, shorten Rx to 8 wk

ILLUMINATE: Naïve RGT, Phase 3: Telaprevir: RGT: 24 vs. 48

REALIZE: Experienced, Phase 3: Telaprevir: Lead-in

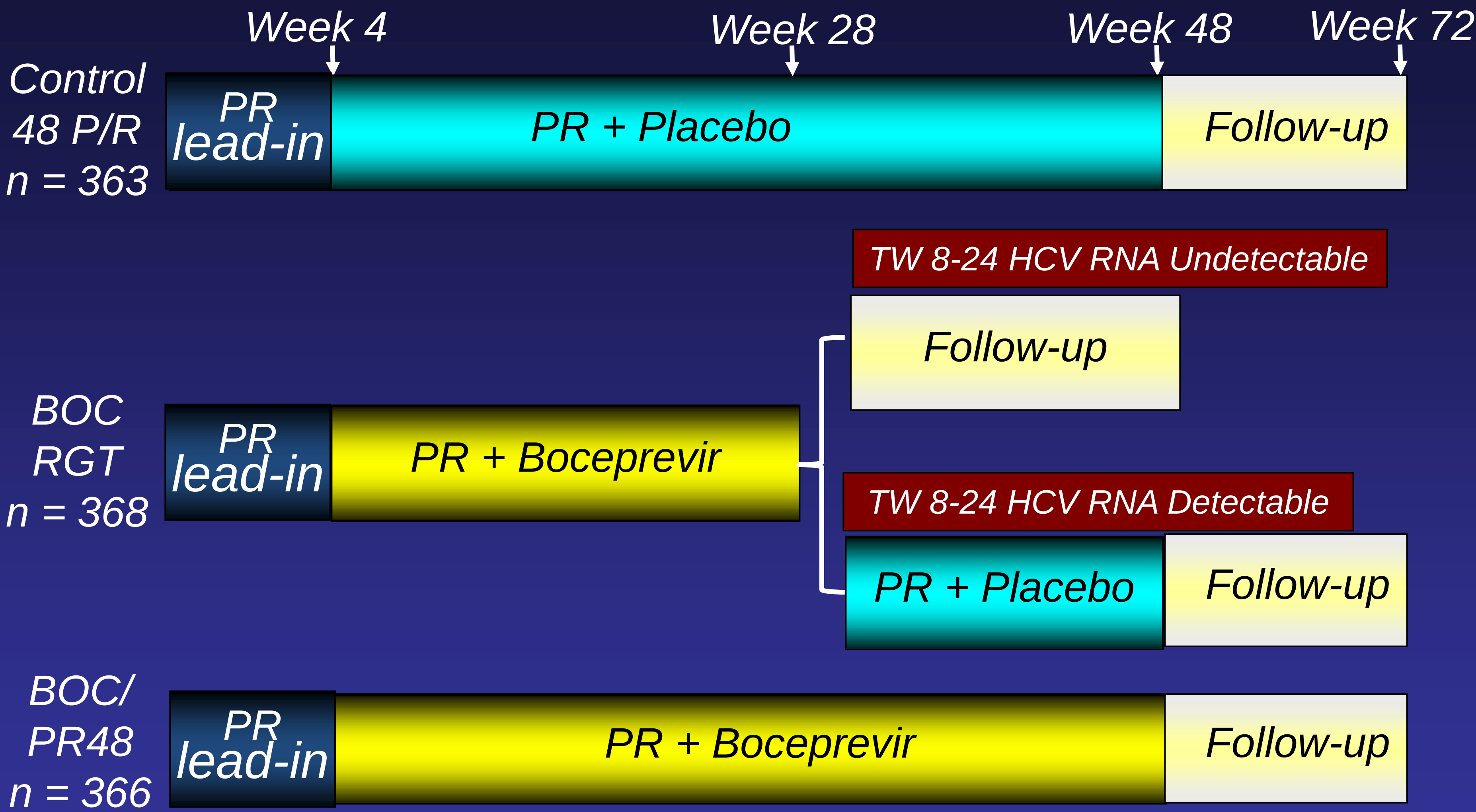
Add on to SOC: Phase 2 Trials of HCV NS3-4A protease inhibitors in HCV-1

Response	PROVE1 (24 wks)	PROVE2 (24 wks)	SPRINT-1 (28 wks) (no leadin/leadin)	SPRINT-1 (48 wks) (no leadin/leadin)	SOC Peg/RBV (48 wks)
RVR	81%	69%	39%	37%	8-15%
SVR	61%	68%	54/56%	67/75%	38-48%

- *PROVE1: TPV + Peg-2a / RBV × 12 wks then Peg/ RBV × 12 wks if RVR (24W)*
- *PROVE2: TPV + Peg-2a / RBV × 12 wks then Peg RBV × 12 wks (24W)*
- *SPRINT-1: Boceprevir + Peg-2b + RBV for 24/28 weeks or 44/48 weeks with or without a 4-wk lead in period of PEG-2b + RBV*

McHutchison J, et al. NEJM 2009;360:1827-38
Hezode C et al, NEJM 2009;360:1839-50
Kwo P, et al. Lancet 2010; 376:705-16

SPRINT-2: Boceprevir in G1 Naïve CHC

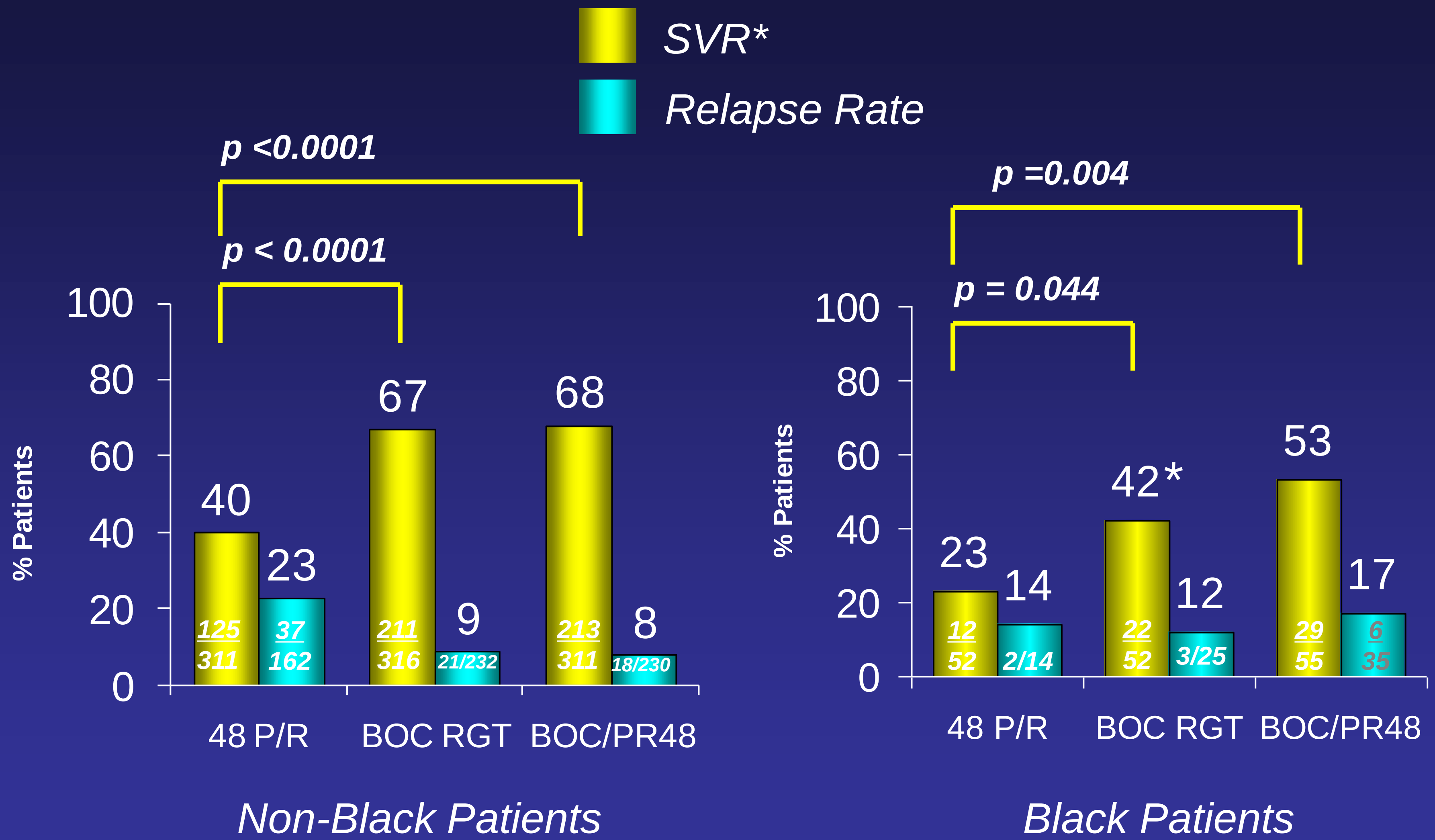


Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg thrice daily

Poordad F et al. NEJM 2011;364:1195-1206

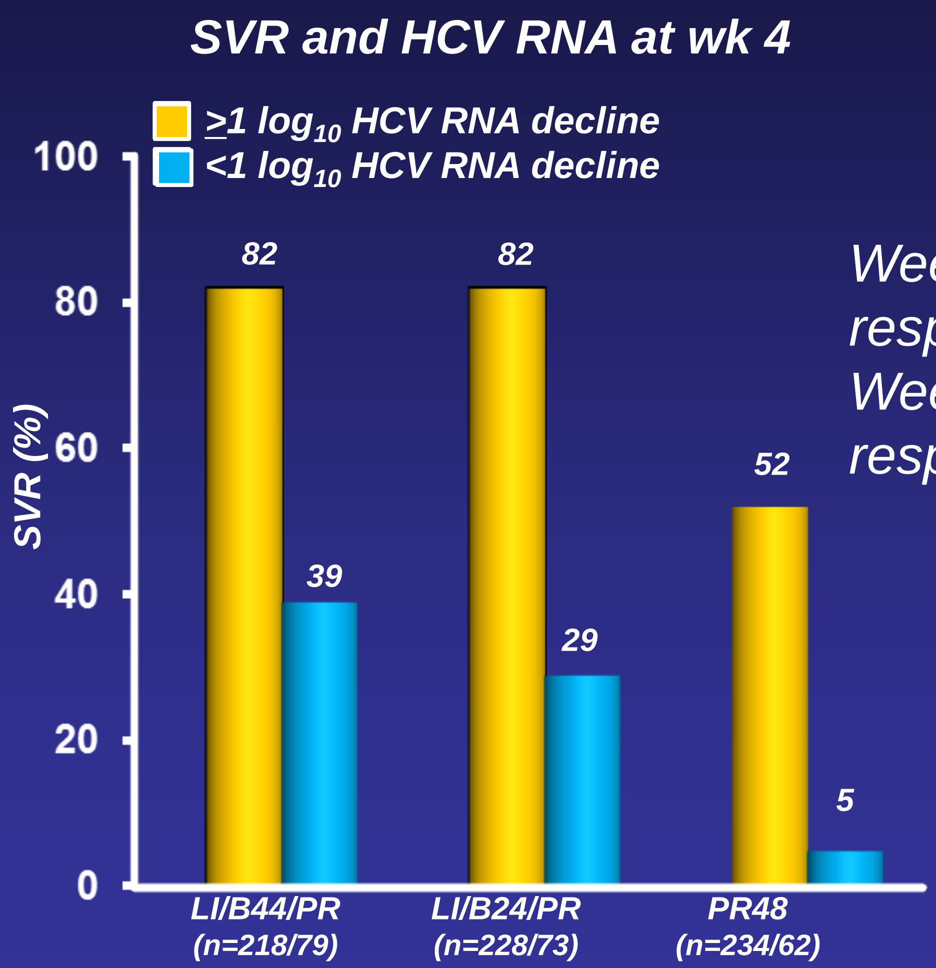
SPRINT-2: SVR and Relapse Rates (ITT)



*(mITT in 47% vs 53%)

Poordad F, et al NEJM 2011;1195-1206

SPRINT-2 Study Outcomes Based on Week 4 Lead-In (Nonblack Patients)

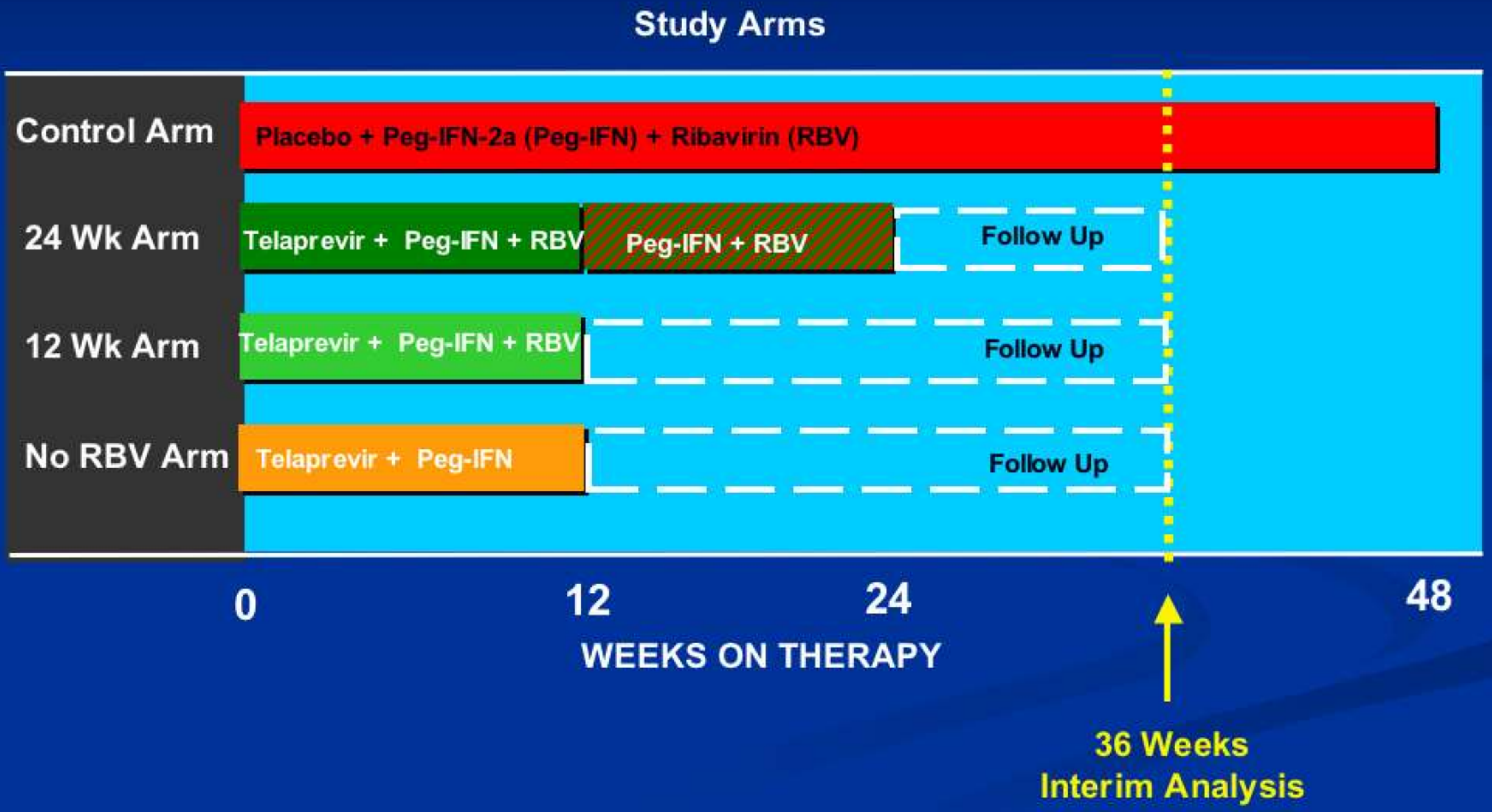


Week 4--1 log response is similar to: Week 12--2 log response

RAVs: resistance-associated variants. Boceprevir RAVs determined with population sequencing.

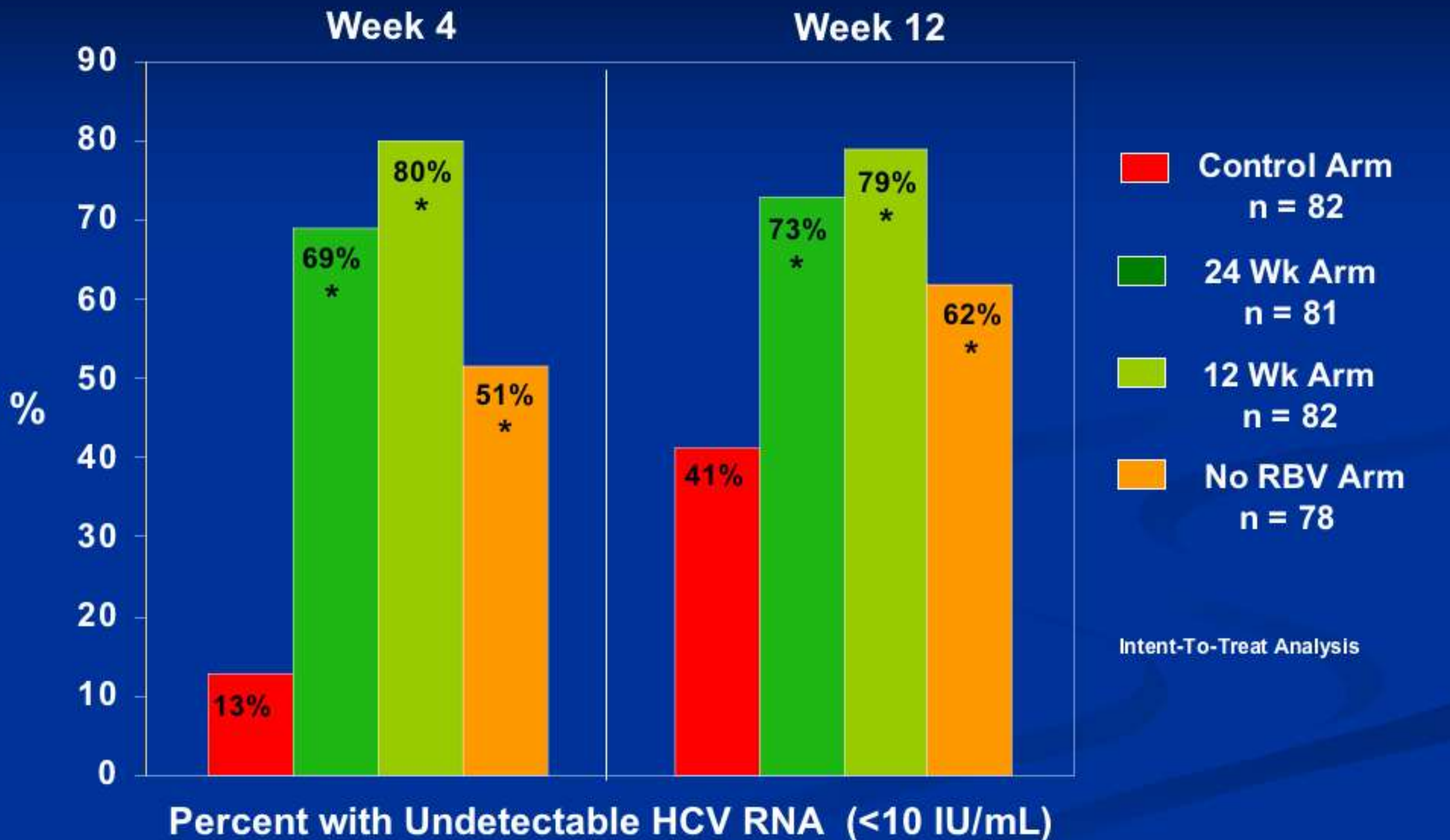
Poordad F, et al. NEJM 2011;364:1195-1206

PROVE2
Study Design



PROVE2

Undetectable HCV RNA at Weeks 4 and 12



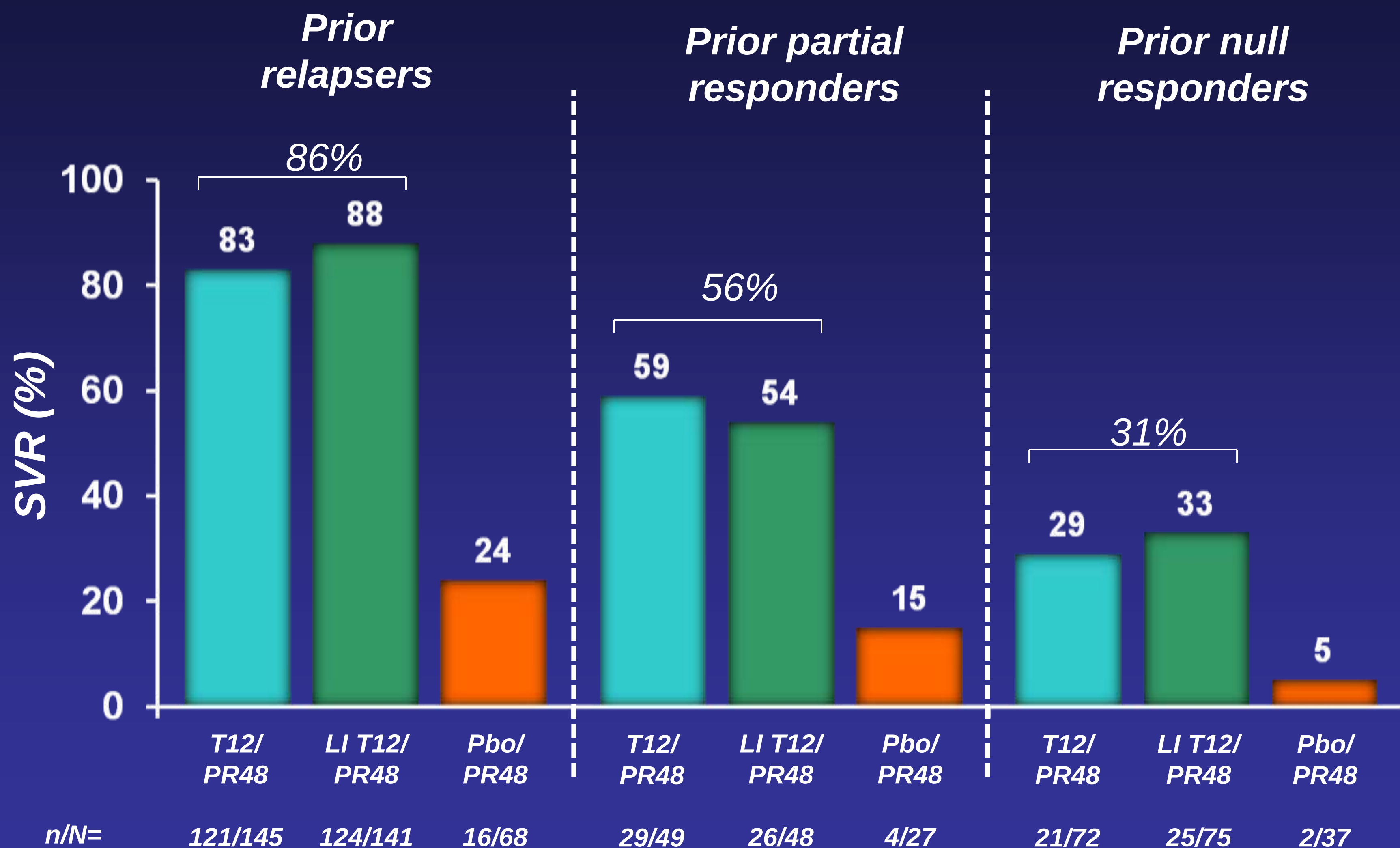
** p<0.001 compared to control arm*

ADVANCE: Most Common Adverse Events

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Any Adverse Event*	99	99	98
Fatigue	57	58	57
Pruritus	**50**	**45**	**36**
Headache	41	43	39
Nausea	**43**	**40**	**31**
Rash	**37**	**35**	**24**
Anemia	**37**	**39**	**19**
Insomnia	32	32	31
Diarrhea	**28**	**32**	**22**
Influenza-like illness	28	29	28
Pyrexia	26	30	24

Shaded areas: 10% or greater incidence in either TVR groups vs control

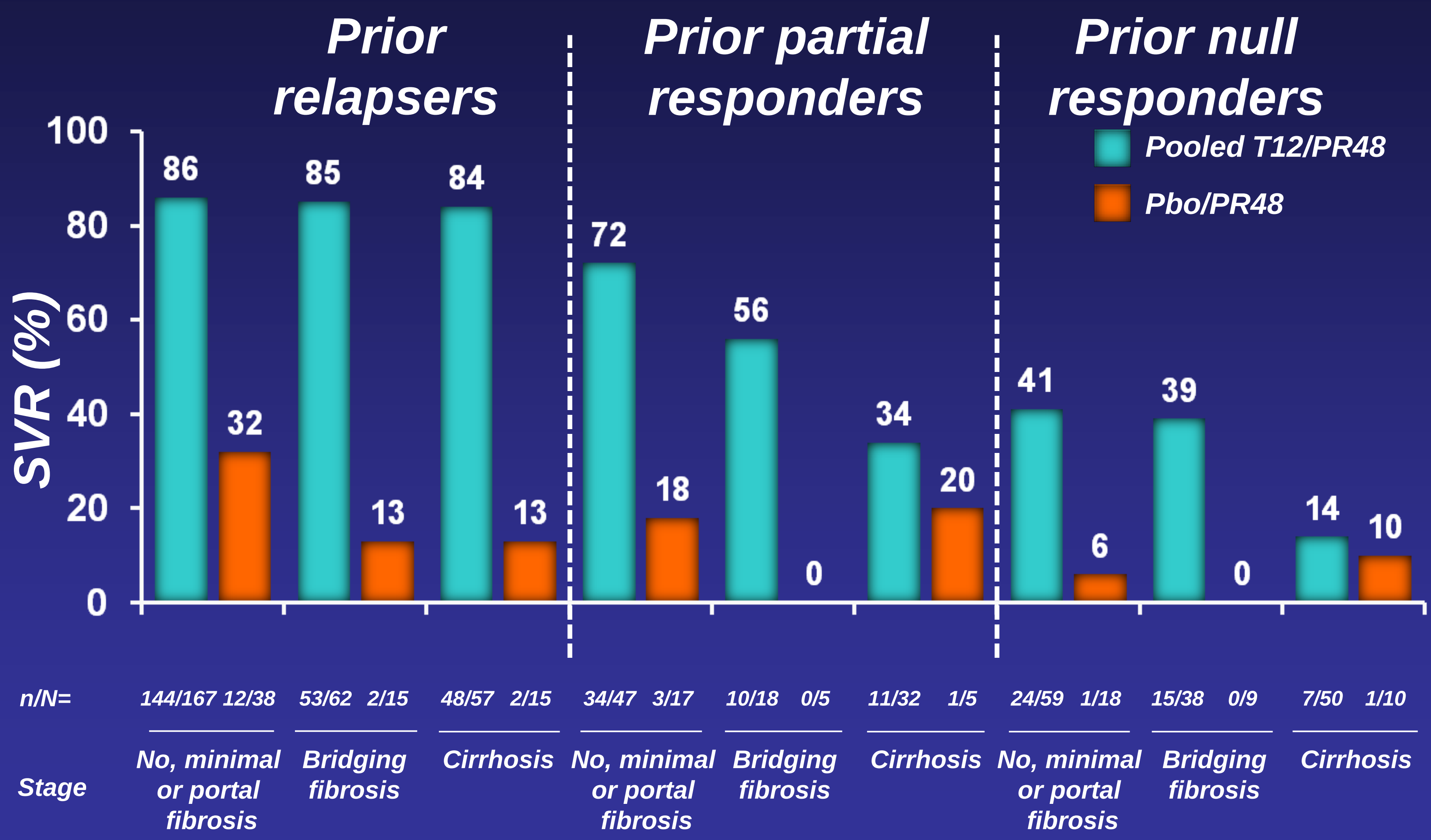
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



Zeuzem S, et al.EASL:2011, Oral Presentation 5.

****p<0.001 vs Pbo/PR48***

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



Zeuzem S, et al.EASL:2011, Oral Presentation 5.

Known Drug Interactions: Both PI's

Pretty certain	Likely
All HIV PI's interact	Cyclosporin/Tacrolimus
Midazolam	Colchicine
Sildenafil/tadalafil	Warfarin
Cisapride	Budesonide/Prednisone
Lovastatin/Simvastatin	Efavirenz, ? NNRTI's
Migraine drugs: ergots	Azoles
Rifampin	Trazodone/Celexa
Anticonvulsants	Most anti-arrhythmics

Conclusions: HCV Therapy 2011

Durability of therapy

- SVR is a cure
- Tailor therapy to early viral response: RGT is effective

Protease inhibitors

- High rates of RVR in naive patients, ca. 65%
  - Can shorten Rx to 24-28 weeks Rx for RVR's
  - Treatment-limiting adverse effects include rash, diarrhea
- More side effects, limiting responses but few relapses
- Virological failure occurs with mutations, ? significance
- Cirrhosis, high VL, genotype less predictive; 1b > 1a
- Prior IFN/RBV response determines 3-drug response
- Need IFN and RBV so far!!
- Watch for earlier and more severe anemia!

Triple Therapy for Hepatitis C Infection in the Real World: Practice Trends Following the Release of Boceprevir and Telaprevir

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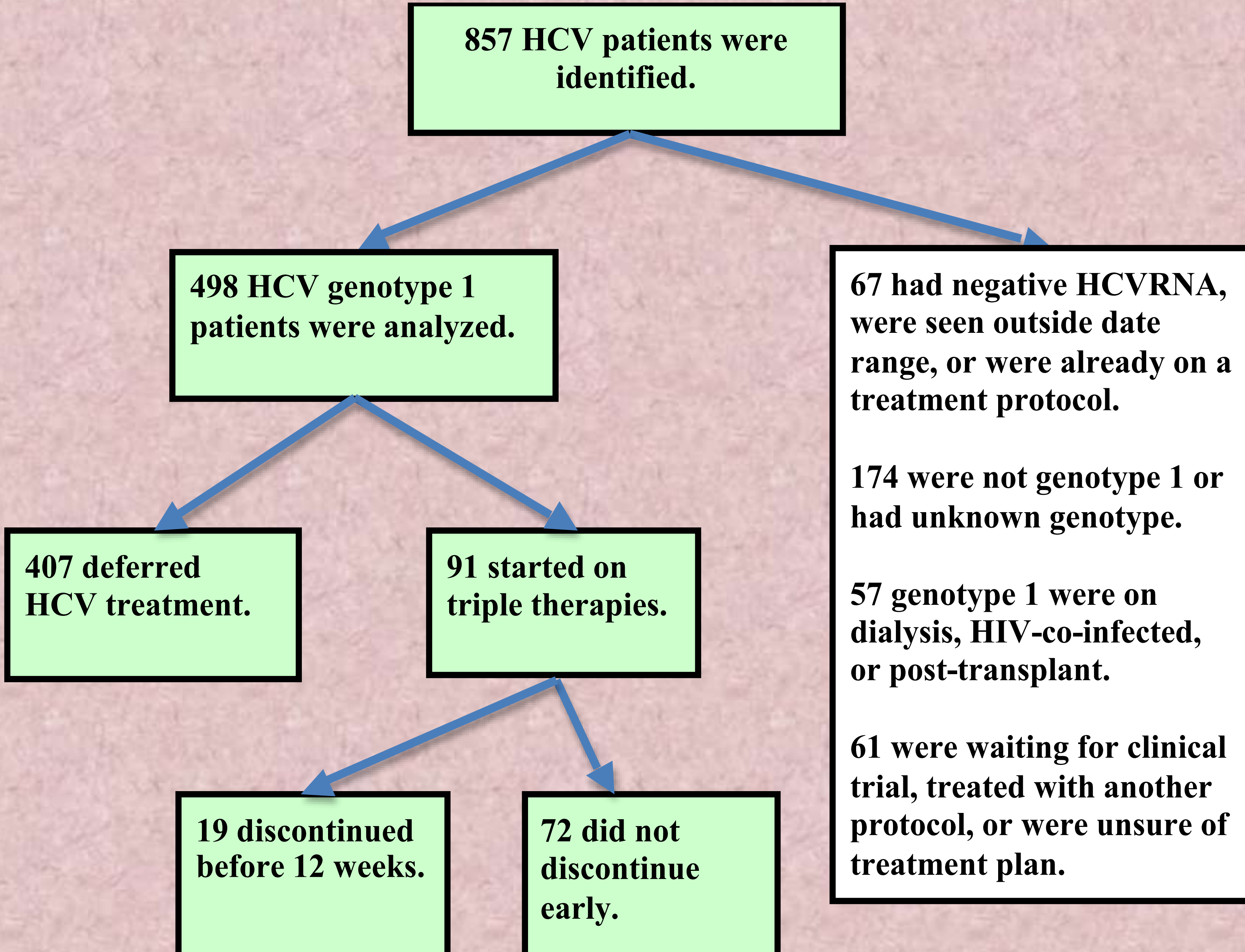
[1]Department of Internal Medicine, Division of Digestive and Liver Disease, University of Texas Southwestern Medical Center, Dallas, TX.

[2]Department of Medicine, Division of Hepatology, University of Miami Miller School of Medicine, Miami, FL.

Aims

- ➢ Determine how many patients accepted/enrolled in triple therapy after approval of DAAs at 2 large academic hepatology practices.
- ➢ Identify factors associated with treatment initiation and deferral.
- ➢ Determine treatment response/discontinuation rates.
- Who is getting treated now? 2011-2012

Results


857 HCV patients were identified.
498 HCV genotype 1 patients were analyzed.
67 had negative HCVRNA, were seen outside date range, or were already on a treatment protocol.
174 were not genotype 1 or had unknown genotype.
57 genotype 1 were on dialysis, HIV-co-infected, or post-transplant.
61 were waiting for clinical trial, treated with another protocol, or were unsure of treatment plan.
407 deferred HCV treatment.
91 started on triple therapies.
19 discontinued before 12 weeks.
72 did not discontinue early.

Results

Table 2a. Predominant reasons for not starting on triple therapy.	
Total N=407	**N (%)**
Contraindications	206 (50.6%)
Patient choice	89 (21.9%)
Early or mild liver disease	69 (17.0%)
Strategy to wait for next generation DAAs	43 (10.6%)

Table 2b. Specific contraindications for not starting on triple therapy.	
Total N=407	**N (%)**
Contraindications	**206 (50.6%)**
Complications of Liver Disease	66 (16.2%)
Medical co-morbidities	63 (15.5%)
Significant adverse events from prior HCV therapy	32 (7.9%)
Psychiatric illness	25 (6.1%)
Advanced age	11 (2.7%)
Substance abuse	6 (1.5%)
Multiple or other contraindications	3 (0.7%)

Discussion

- Triple therapy initiation rate was only 18%
- Reasons to defer triple therapy included medical and psych contraindications, too early or too late
- Probably more HCV patients in academic practices have advanced fibrosis and/or are prior treatment non-responders. "Hard-to-treat"
- Triple therapy discontinuation rate (20.8%) higher than the 7-9% reported in clinical trials

Discussion

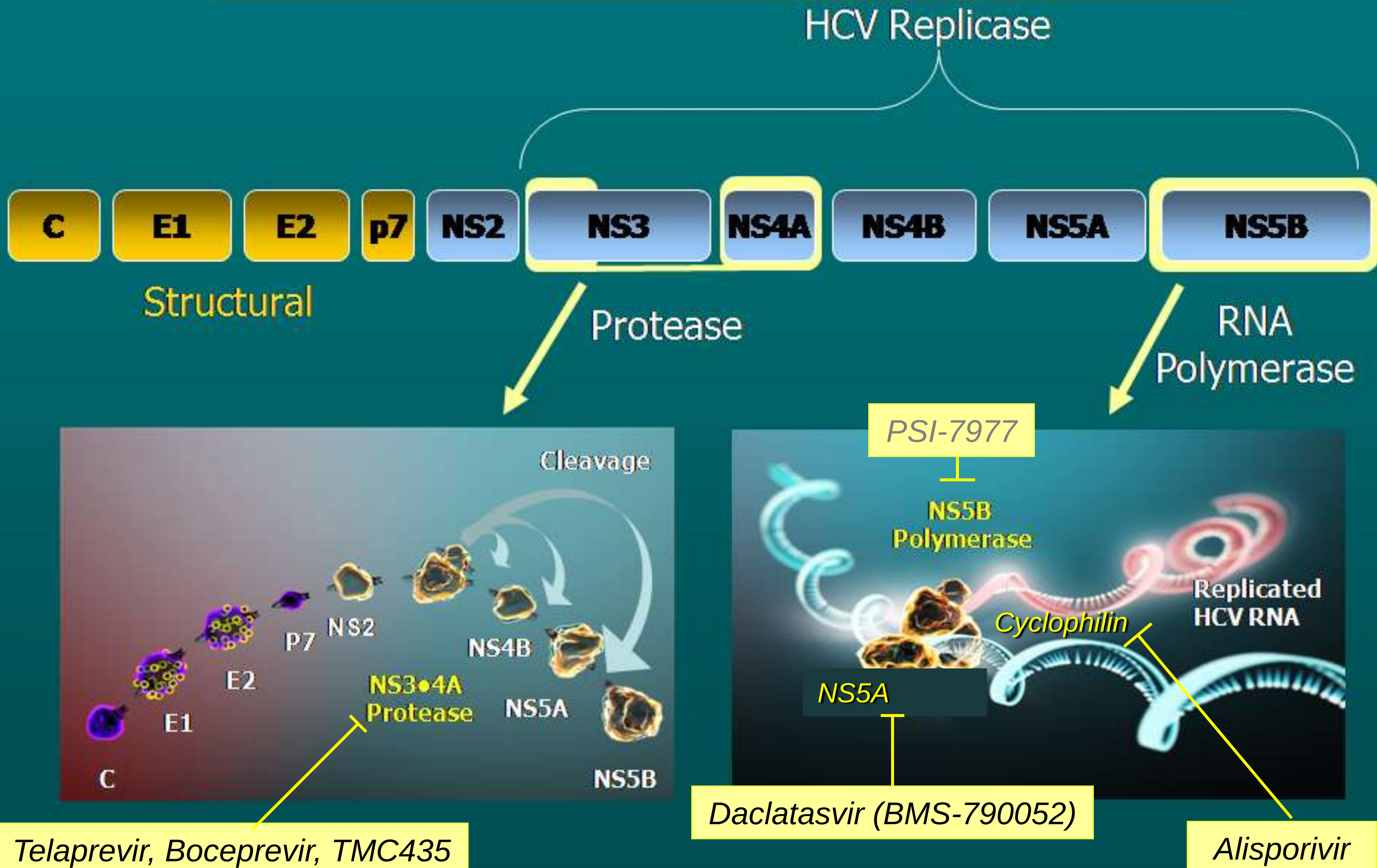
Study Limitations:

- The two study sites had different populations including demographics, clinical characteristics, and provider preferences.
- Missing data inherent in retrospective medical chart review study design was unavoidable.
- Treatment deferral group contained heterogeneous populations.
- Treatment completion and SVR data were not yet available.

Conclusions

- Despite improved efficacy with triple therapy, HCV treatment initiation rates are relatively low/unchanged.
- Limitations of current therapy include side effects and lack of efficacy in prior non-responders
- Estimated SVR compared to screen rate = 15%
- We need more effective and tolerable therapy for HCV genotype 1 patients, especially for those who have cirrhosis and who had prior treatment non-response.

HCV Enzymes Provide Good Targets for Drug Development

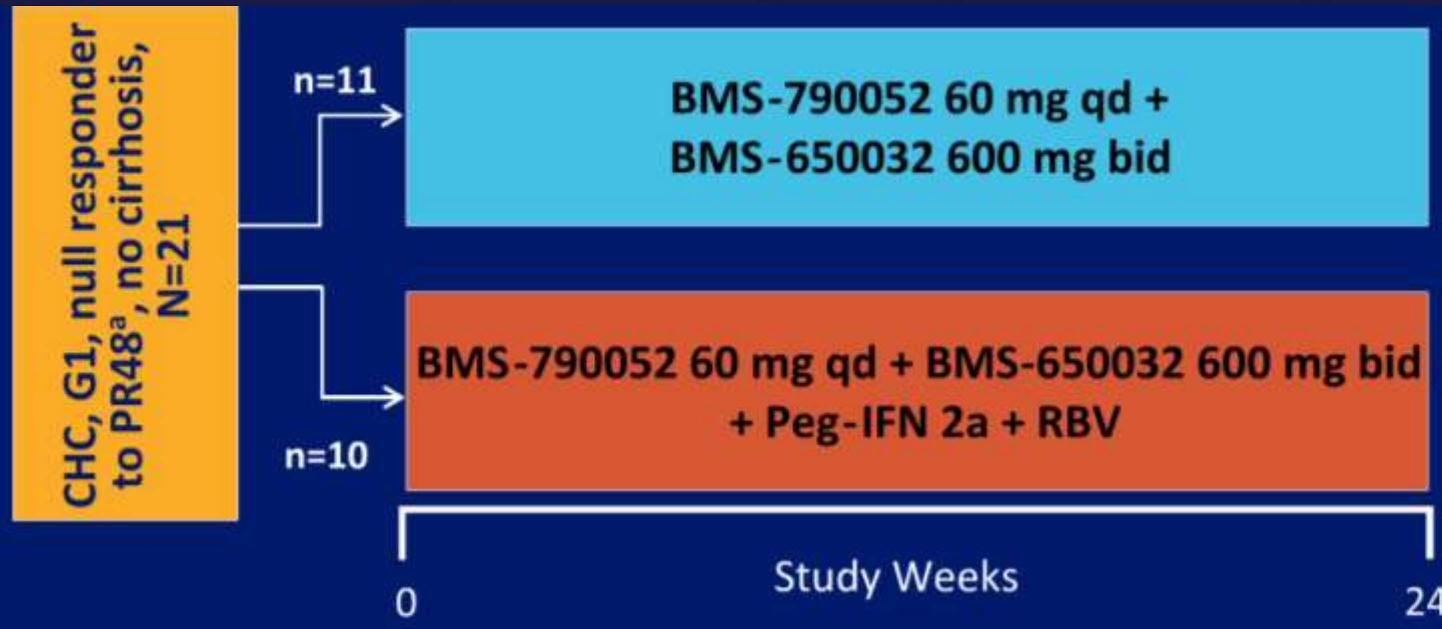


Adapted from Kwong AD. *Curr Opin Pharmacol.* 2008; 8(5): 522-31

Examples of > 80% SVR Rates in Phase II, DAA + PegIFN + RBV Trials in HCV GT1, Rx Naive Patients

Direct Acting Antiviral	Target	SVR rates (DAA /PR vs. PR)	Unique Features
Daclatasvir 10 mg, 48 wk, N=12	NS5A Replication Complex	92% vs. 25%	First in class Once daily dosing No new side effects
TMC435, 150 mg X 24 wk, N=79	NS3/4A protease	86% vs. 65%	Macrocyclic Higher resistance barrier Once daily dosing
PSI-7977 400 mg, 24 wk, N=47	NS5B polymerase	91% vs. < 50%	Pangenotypic Once daily dosing No resistance observed

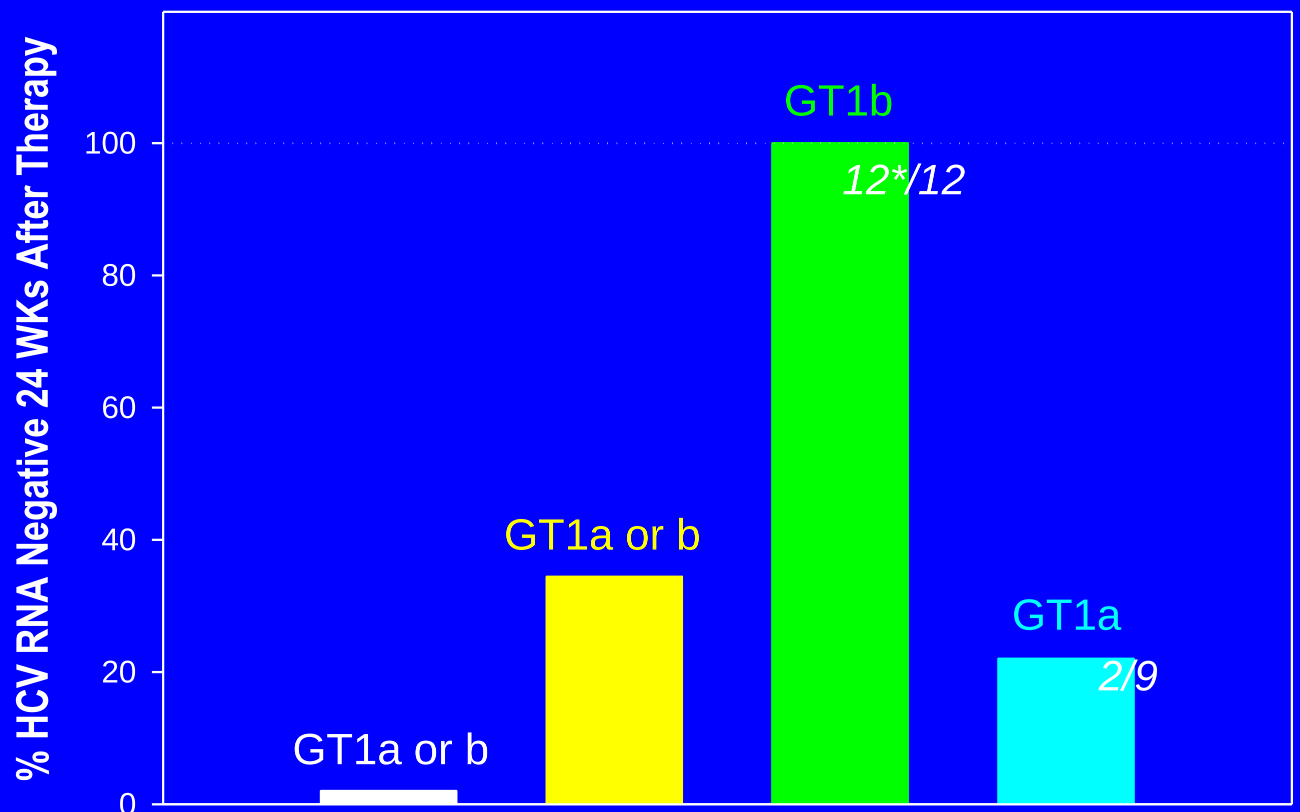
Phase 2a Study of Double or Quadruple Therapy of Null Responder, Genotype 1 HCV Infection with Daclatasvir (BMS-790052) and Asunaprevir (BMS-650032) +/- PR



	IL28B CT/TT	1a/1b	RVR	EOT	SVR12
PI + NS5A	90.4%	9/2	63.6%	45%	36%
Quad		9/1	60%	100%	100%

Lok, AS, et al, NEJM, 2012; 366:216

Cure of Genotype 1b, Prior Null-Responder HCV Infections with an Interferon-Free Regimen

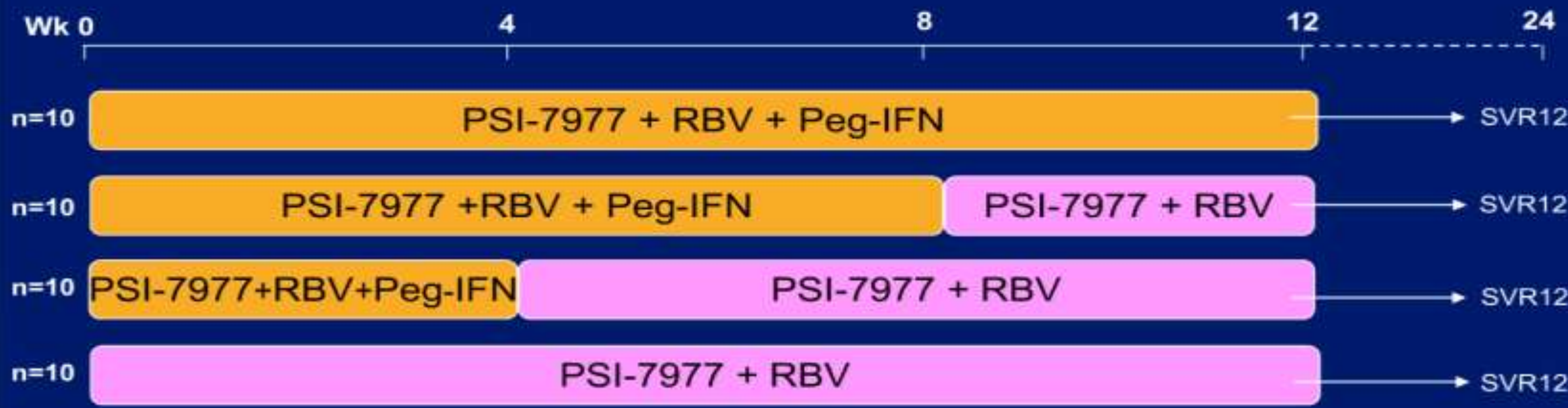


PEG Interferon, WKs:	48	48	0	0
Ribavirin, WKs:	48	48	0	0
DAA, WKs:	0	12, TVR	24, Daclatasvir 24, BMS 650032	

Zeuzem, S., et al, N. Engl. J. Med., 2011, 364:2417
Lok, A.S., et al , NEJM, 2012; 366:216
Chayama, K. et al, Hepatology, 2011; 54:1428A

**One patient completed only 8 weeks RX but still HCV RNA negative 24 wks later*

PSI-7977 ELECTRON
Nucleotide Analogue in Genotype 2/3



Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
SVR12	11/11	**100**	10/10	**100**	9/9	**100**	10/10	**100**

HCV GT2 or GT3, open-label

- 25 treatment-naïve patients with HCV GT2 or GT3; one pt lost to F/U after Day 1
- 24/25 RVR, SVR 12 and SVR 24 (EASL 2011, Lalezari *et al.*)

The ATOMIC Study; 7977 plus P/R for geno 1 HCV

Summary: Current State of Play 2012

- Triple therapy is superior to Peg/RBV
- But is not successful in many patients with established cirrhosis
- Interferon/RBV still needed so far – in 2012
- New agents hold great promise/not here yet
- We will be able to treat all sorts of HCV patients within the next 3 years: HIV, cirrhosis, post-transplantation

Unanswered Questions

- 2nd generation agents are not yet here but seem amazing
- Will they work as well in the ‘hard to treat?’
- How will we treat HIV/HCV? Or transplant patients?
- When will we have an approved IFN-free regimen?
- What will be the cost of a ‘sure cure?’

Public Health Concerns

- Medications very expensive, currently up to $70,000 for a course of treatment
- No vaccination available
- Large number of unrecognized cases, probably around 50%
- Need to develop strategies to identify new cases
- Increasing numbers with end-stage liver disease being recognized: HCC
- Large burden on health care system

Taking the CDC Recs to Heart

- CDC recs represent a watershed
- How to implement them?
- How about employee screening for HCV?
- HIPAA considerations?
- The drugs will soon be available
- Conquering Hep C is in sight!!

UT Southwestern
Clinical Program in Hepatitis

Routine care, chronic liver disease, difficult to treat patients, clinical trials, drug-induced liver injury, hepatitis B and C

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